THE PROGNOSTIC SIGNIFICANCE OF MULTI-MODALITY EVOKED

RESPONSE TESTING IN HIGH RISK NEWBORNS

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ABSTRACT

In a previous prospective study from our laboratory, the prognostic significance of the auditory brainstem evoked response (ABR) was assessed in high risk neonates. An abnormal ABR predicted neurologic sequelae at 1 year; however there were false negatives. In this study, somatosensory evoked responses (SER) were performed together with the ABR so that a wider distribution of the nervous system could be evaluated. Testing was carried out on healthy and high risk neonates in the newborn period and in infancy. Infants were subsequently evaluated in a blind fashion at 1 year of age by a pediatric neurologist and psychologist. As part of this study, normative data and reliable testing procedures needed to be established. The effect of gestational age on evoked responses performed in the newborn period was also determined

The results demonstrated that the ABR and SER can be reliably recorded in newborns. Latency and morphological changes on serial testing reflected maturation of the nervous system. Chi square analysis revealed that an abnormal SER or ABR predicted neuromotor impairment at 1 year of age. The type of SER abnormality further delineated the degree of disability. A normal SER and ABR predicted normal neurodevelopmental outcome. In conclusion, multi-modality evoked response testing yielded valuable prognostic information for the newborn at high risk for neurologic sequelae.

RÉSUMÉ

Dans une étude prospective précédente, nous avons évalué
la valeur pronostic des potentiels évoqués auditifs dans une
population de nouveau-nés à haut risque. Advenant des potentiels
évoqués auditifs anormaux, des séquelles neurologiques étaient
prévisibles à un an; toutefois, il y avait des faux négatifs.
Dans l'étude actuelle, les potentiels évoqués somato-sensitifs
ont été étudiés parallèlement aux potentiels evoqués auditifs
de façon à obtenir une évaluation plus globale du système nerveux.
La population étudiée comparait des infants normaux de même que
des enfants à haut risque de la période néo-natale à la petite
enfance. Les enfants étaient réevalués, a simple insu à l'âge
d'un an par un neurologue et un psychologue. Au cours de cette
étude, des données normatives ainsi que des méthodes d'évaluation
fiables devaient être établies. L'effet de l'âge gestationnel
sur les potentiels évoqués obtenus dans la période néo-natale
a également été évalué.

Les résultats de l'étude ont démontré que des potentiels
évoqués auditifs et somato-sensitifs peuvent être enregistrés
de façon fiable chez les nouveau-nés. Les variations au niveau
de la latence ainsi que les changements morphologiques, sur des
enregistrements sériés reflètent la maturation du système nerveux.
L'analyse du Chi carré révèle que des potentiels évoqués auditifs
et somato-sensitifs anormaux permettent de prédire une atteinte
neuromotrice à un an de vie. Le type d'anomalie documentée au
niveau des potentiels évoqués somato-sensitifs permet de préciser
davantage le degré d'incapacité. Des potentiels évoqués auditifs
et somato-sensitifs normaux, permettent de predire un dévelopment
neurologique normal.

En conclusion, une étude multi-modale des potentiels évoqués
a une valeur pronostic valable dans l'évaluation des nouveau-nés
à risque de séquelles neurologiques.

ABBREVIATIONS

attention deficit disorder	ADD
auditory brainstem evoked response	ABR
central nervous system	CNS
cerebral palsy	CP
cervical vertebra II	CII
computed tomography	CT
Einstein Neonatal Neurobehavioral Assessment Scale	ENNAS
electroencephalography	EEG
Erb's point	EP
intrauterine growth retardation	IUGR
magnetic resonance imaging	MRI
minimal brain dysfunction	MBD
National Collaborative Perinatal Project	NCPP
neonatal intensive care unit	NICU
Neurological and Adaptive Capacity Score	NACS
periventricular leucomalacia	PVL
small for gestational age	SGA
somatosensory evoked response	SER
very low birthweight	VLBW
visual evoked response	VER

PREFACE

Perinatal brain damage as a result of hypoxic-ischemic injury is common in the neonatal intensive care unit (NICU) population, and therefore a matter of significance in perinatal care. Exposure to hypoxic-ischemic events in fetal or neonatal life may lead to permanent brain injury and subsequent neurodevelopmental deficits. The damage to the brain may be focal, patchy or diffuse and appears to be dependent on the type and timing of the insult.

Several clinical investigators have designed studies that attempt to predict which ICU graduates are most at risk for permanent brain damage. Some infants appear to "recover" from an insult to the brain whereas others with similar injuries either die or suffer significant neurologic sequelae. At present, it is difficult to accurately predict outcome in this population. Therefore clinicians must follow and observe children with a history of perinatal encephalopathy over the first years of life, to ensure that developmental deficits are identified early and various treatment modalities may be initiated before secondary complications are evident.

Clinical and diagnostic tools have been somewhat helpful in identifying an at risk group, particularly in those that have sustained a significant neurologic insult. However a better neurologic profile incorporating several predictive factors is needed to reliably identify what constitutes "high risk". Predictive studies using

diagnostic tests have focused on cerebral imaging techniques that examine structural changes in the immature nervous system following perinatal injury. Evoked potential studies are non-invasive electrophysiologic tests that measure the functional integrity of ascending pathways of the nervous system. In a prospective study in our laboratory, the neonatal auditory brainstem evoked response (ABR) was found to have a high specificity and positive predictive power for neurologic status at 1 year of age. False negatives were a problem , as the ABR appeared to be sensitive to one pattern of anoxic-ischemic injury involving brainstem structures as well as other structures of the central nervous system (i.e. selective neuronal necrosis). However other patterns of injury do occur, that may not significantly involve the auditory relay nuclei. Therefore using multi-modality evoked responses, such as the somatosensory evoked response (SER) as well as the ABR, a larger area of the nervous system could be functionally evaluated, hopefully minimizing the false negative findings.

The prospective study reported in Chapters 1-4 examines the prognostic significance of multi-modality evoked responses in high risk newborns. High risk newborns as well as healthy full term neonates were evaluated in the newborn period and in infancy (2 and 6 months of age) with the ABR and SER. The study group and the controls were subsequently evaluated in a blind fashion by a pediatric neurologist and clinical psychologist to determine outcome

at 1 year corrected age. As part of this project, appropriate normative data needed to be established. The effect of gestational age on evoked responses performed in the newborn period (approximately 40 weeks conceptional age) was determined as well.

The results of this prospective study demonstrate that the ABR and SER can be reliably recorded in newborns. This study emphasizes the importance of using conceptional age as opposed to chronological age when interpreting evoked responses in young infants. Maturational changes on serial testing included a decrease in central conduction time as well as waveform duration, and an increase in peak amplitudes. Chi square analysis revealed that an abnormal SER or ABR was strongly predictive of neuromotor impairment at 1 year of age. The type of SER abnormality further delineated the degree of subsequent disability. A normal ABR and SER predicted normal neurodevelopmental outcome with a strong negative predictive power. In conclusion, the findings of this study suggest that multi-modality evoked response testing in the newborn period and in infancy yields valuable prognostic information for the newborn at high risk for neurologic sequelae.

INJURY TO THE IMMATURE NERVOUS SYSTEM

Asphyxia neonatorum refers to an impairment in the exchange of respiratory gases during parturition. Hypoxic-ischemic damage to the maturing neural tissue occurs as a result of the deficient supply of oxygen to the brain. The subsequent neurologic outcome may include death in utero or in infancy, major handicap such as cerebral palsy, mental retardation, blindness, deafness, or epilepsy, or minor handicap such as developmental deficits, behavior disorders or learning disabilities (Perkins, 1987; Volpe, 1987; Windle, 1968). Aspnyxia may result from hypoxia (diminished oxygen in the blood supply) and/or ischemia (diminished blood perfusing the brain). A deficient supply of oxygen affects brain energy metabolism as anaerobic respiration is highly inefficient in meeting the energy demands of the brain. Depletion of energy stores, accumulation of lactic acid and disturbance of the blood brain barrier occur following persistent anaerobic metabolism (Raichle, 1983). As a result, structural injury of the immature nervous system rapidly ensues (Hill & Volpe, 1981; Volpe, 1987). This relationship between early anoxic-ischemic insult and subsequent cerebral damage has been well substantiated by both animal experimental data and human neuropathological studies (Myers, 1975; Volpe, 1987 ;Windle & Becker, 1943).

Hypoxic-ischemic injury can occur in the prenatal, perinatal, or early postnatal periods. Brain development

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rapidly begins after conception and at this time the organism is most vulnerable to major insults, when fundamental structures are forming. Midway through fetal life, most neurons have been generated (Perkins, 1987). Concomitent with neuronal multiplication and cell migration and organization, there are blood flow changes and alterations in vasculature. For example, there are alterations in regional dominance of blood supply. At 24-28 weeks gestational age, the periventricular germinal matrix is highly vascularized. But as the fetus approaches full term (40 weeks gestational age), the blood supply is directed primarily to the developing cortex and underlying white matter (Volpe, 1987). Therefore, with development of the central nervous system, the functional activity and energy metabolism shifts to meet the demands of the areas that are actively differentiating. Myelination and glial differentiation characterize the late stages of fetal development and continue into postnatal life (Norman, 1975; Perkins, 1987). Therefore the timing of the hypoxic-ischemic insult to the developing nervous system is critical, and will influence the extent and location of the damage to the brain.

The etiology of perinatal brain damage is multifactorial (Moore, 1986). Hypoxia is often unidentifiable prior to birth but may be related to maternal factors such as hypotension or inhalation of poisonous gases; or fetal factors such as umbilical cord prolapse,

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placenta previa or an abruptio of the placenta. Prolonged, difficult deliveries may predispose to hypoxic events. Neonatal hypoxic insults may occur with respiratory distress syndrome, apnea, chronic pulmonary insufficiency and cardiac arrest. These early postnatal hypoxic episodes are particularly prevalent in premature infants of very low birthweight (Norman, 1975). Ischemia or hemorrhage may result from hypotensive or hypertensive states or cardiorespiratory immaturity or insufficiency (Moore, 1986). For example, rupture of the delicate vessels of the periventricular germinal matrix in premature infants results in intraventricular hemorrhage and subsequently, the adjacent brain tissue is vulnerable to necrotic damage. Periventricular leucomalacia is a nonhemorrhagic, symmetric lesion that is also characteristically seen in premature infants, and is apparently due to ischemic injury to the white matter (Volpe, 1989a). Mechanical injury following traumatic delivery may result in a hematoma or tentorial tears (Norman, 1975). Intrauterine growth retardation (IUGR), which may disturb normal brain development, occurs when the fetus is deprived of adequate nutrition. This may be due to uteroplacental insufficiency and/or the mother's dietary habits (Perkins, 1987). Exposure to infectious agents such as toxoplasmosis, rubella, herpes and cytomegalovirus, as well as environmental hazards such as alcohol, drugs, radiation and chemicals, are potentially deleterious to the normal formation of brain tissue.

Finally, there is cerbral dysgenesis, which may be inherited or occur by mutation(Perkins,1987; Volpe, 1987).

It has become increasingly evident that each fetus tolerates teratogens or exposure to hypoxic or ischemic events differently (Wigglesworth, 1984). It appears that some fetuses have an enhanced susceptiblity to brain injury whereas others are remarkably resilient. For example, in a large prospective study involving approximately 40,000 infants (the National Collaborative Perinatal Project-NCPP), the majority of survivors of severe neonatal depression (defined as an Apgar score < 4 at 5 minutes) were neurologically normal by 7 years of age (Nelson & Ellenberg, 1981; Perkins, 1987). Therefore, some infants may tolerate a brief, acute insult well, without neurologic sequelae. Those who suffer injury may have a genetic predisposition or may have already been neurologically compromised in utero. Brain damage may occur without difficult labor or clinical evidence of perinatal asphyxia. Conversely, severe difficulties during the delivery and severe postnatal hypoxia are usually not followed by brain damage (Illingsworth, 1985; Perkins, 1987). Freud in 1897 proposed that "the anomaly of the birth process, rather than being the causal etiologic factor, may itself be the[1] consequence of the real prenatal etiology". Current literature suggests that brain injury or maldevelopment prior to birth is significantly underappreciated and the current epidemic of obstetrical malpractice suits clearly

reflects this (Nelson & Ellenberg,1986; Perkins, 1987).

PATTERNS OF PERINATAL BRAIN INJURY

Disturbance of oxygen supply to the developing nervous system may cause destructive changes. There are a variety of pathogenic mechanisms described in both animal and human studies of perinatal brain injury, however the specific pathogenesis for the individual fetus or infant is often unknown (Rorke, 1982; Wigglesworth, 1984). Oxygen deficits following hypoxic-ischemic insult lead to anaerobic respiration. Consequently, energy stores are depleted quickly, lactic acid accumulates and there is structural damage to brain tissue (Rorke, 1982). Severe hypoxia may cause widespread necrosis (i.e. encephaloclastic lesions). Mild to moderate deficiencies in oxygen supply may result in focal, multifocal, or diffuse injury, with characteristic scarring or cystic changes (Towbin, 1971). Acute hypoxic lesions are proceeded by system circulatory failure such as venous congestion in organs, cyanosis, cardiac dilatation, peripheral edema and cardiac decompensation. As a result of local venous stasis and thrombosis, there may be further infarctional damage to organs with high blood flow volume such as the brain, kidneys and adrenal glands. In summary, circulatory insufficiency often ensues secondary to the hypoxic event and may further aggravate the existing lesion to the brain (Perkins, 1987).

There are several patterns of anoxic-ischemic injury to

the nervous system that may result in specific histopathological changes and concommitant neurological manifestations. Many experimental models of perinatal brain damage in animals have been proposed to further our understanding of the role of asphyxia in the etiology of neurodevelopmental defects in humans.

In early experiments by Windle & Becker in 1943, the uterine vessels or umbilical cords of fetal guinea pigs were occluded with a clamp for varying lengths of time. Fifty-eight animals were delivered once intrauterine respiratory movements became weak whereas another 45 animals ceased all respiratory efforts prior to being delivered. Ninety litter mates served as controls to the 103 experimental anoxic animals. Induced anoxia prenatally was followed by "asphyxia pallida", characterized by apnea, bradycardia, atonia, dilation of the capillary beds and pale cold skin. The degree of anoxia did not correlate with the severity of brain damage. Sixty-five percent of the experimental animals showed diffuse histopathologic changes such as edema, chromatolysis, necrosis, and enlarged ventricles. Glial proliferation was most apparent by the second week of life (Windle & Becker, 1943).

Neuropathology of asphyxia neonatorum in a primate was first described by Ranck & Windle in 1959. Asphyxiation of monkeys near term (Macaca mulatta) was achieved by detachment of the placenta with fetal membranes intact, and subsequent delivery 11-16 minutes later with resuscitation.

Pathologic examination revealed marked destruction of the inferior colliculi. Other areas of injury included the gracile and medial cuneate nuclei, the roof of the cerebellum, the putamen, globus pallidus, ventral posterior region of the thalamus, principal oculomotor nucleus, superior and medial vestibular nuclei, superior olives, as well as principal sensory and spinal trigeminal tract nuclei. Lesions were generally bilaterally symmetrical and appeared on the second as well as the 9th day of life Manifestations of the injury included cytolysis of neurons as well as the neuroglia. In summary, thalamic and brain stem nuclei were more severely affected than cortical structures after perinatal anoxic insult. Chronic lesions in older monkeys were characterized by astrocytic and microglial changes, with white matter as well as the gray matter damage seen acutely (Ranck & Windle, 1959).

Hall examined the sensitivity of the auditory system to hypoxia by examining the brains of 60 fatally asphyxiated newborns, and 30 hypoxic kittens. The asphyxiated infants displayed acute swelling and severe cell degeneration in the brain stem, primarily in the cochlear nuclei, although the superior olives and inferior colliculi were damaged as well. The kittens showed no signs of injury to the auditory pathway, and Hall concluded that kittens were highly resistent to low oxygen in the atmosphere. It is more likely that the pattern of asphyxiation differed among the infants and the kittens, resulting in different pathologic

injury sites (Hall, 1964).

Myers describes four separate patterns of asphyxia in the fetal or newborn monkey.

I. Total asphyxia, which is characterized by a complete cessation of respiratory gas exchange, caused rapid alterations in blood pressure and respiration, decreased pH (acidosis), and pO_2 (hypoxia) and increased CO_2 (hypercarbia). Monkeys resuscitated within 20 minutes of the onset of asphyxia were most likely to survive, however the first evidence of brain injury appeared after 12-13 minutes of total asphyxia. The most vulnerable structures were the inferior colliculi however there was also damage to the superior olives, Purkinje cells, vestibular nuclei, posterior and lateral ventral nuclei of the thalamus, and the gracile and cuneate nuclei. Cortical structures were not involved with this pattern of asphyxia (Myers, 1975).

II. Prolonged partial asphyxia with diminished respiratory gas exchange caused a diminution of oxygen and concommitant increase in carbon dioxide with respiratory and metabolic acidosis. There was marked brain swelling with diffuse hemorrhagic necrosis of the entire cortex or the injury may have been restricted to the posterior parietal regions. The damage may have affected one hemisphere more than the other.

III. Oligoacidotic hypoxia or partial asphyxia without

major alterations in carbon dioxide or pH occurred when the respiratory gas exchange was altered gradually and over longer periods of time. This form of insult led to perivenular white matter hemorrhage with discrete foci of periventricular necrosis and scarring of the white matter in the posterior parietal regions.

IV. Animals suffering from partial plus total asphyxia at delivery showed major lesions to the caudate nuclei, the putamen and globus pallidus, and lesser injury to the neocortex in the region of the intraparietal sulcus, superior angle of the insula and the Sylvian fissure. Therefore partial followed by total asphyxia caused significant injury to the basal ganglia with less conspicuous lesions of the brainstem (total asphyxia) and the cortex (partial asphyxia) (Myers, 1975).

In summary, experimental work of Ranck & Windle, Myers and others have demonstrated that specific structures of the brainstem, thalamus, and cortex are vulnerable to necrotic injury post asphyxia. Myers emphasizes that the character of the insult determines the extent and location of subsequent injury to the nervous system Ischemic and hypoxic cell changes occur in regions of selective vulnerability.

Windle (1968) described the progressive deterioration of brain structures following perinatal brain injury in primates. Three to nine years following the initial insult, pathology revealed widespread depletion of neurons in

regions unaffected initially. Depletion of nerve cells were observed in the third and fourth layers of the postcentral gyri, as well as subcortical structures such as the thalamus, basal ganglia, reticular formation and dorsal column. Clinically, there was both physical and behavioral improvement in spite of the lack of structural repair in brain tissue.

The neuropathologic entities or models of anoxic-ischemic encephalopathy in humans that are summarized in the literature include: 1) selective neuronal necrosis 2)status marmoratus 3)parasagittal cerebral injury 4)periventricular leukomalacia 5)focal ischemic brain injury (Volpe, 1987). Selective neuronal necrosis, which is the most common pattern of injury seen in neonates, involves widespread necrosis of neurons (Griffiths & Laurence, 1974; Hill & Volpe, 1981). Following hypoxic insult, swelling and disorganization of the neuronal mitochondria (Norman, 1975) with little alteration to non-neuronal cells have been reported (Kim, 1975). Patchy cell necrosis with intact myelin, hypertrophied astrocytes and gliosis occur several days later (Norman, 1972; Norman, 1975). Major lesion sites include the hippocampal neurons of the cerebral cortex as well as pre and postcentral cortices, and selective regions of the diencephalon, basal ganglia, cerebellum and brainstem (Brierley et al, 1973; Griffiths & Laurence, 1974; Norman, 1972; Norman, 1975; Volpe, 1981). To date, there are no satisfactory diagnostic

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procedures that can assess the extent of neuronal necrosis in the neonatal period (Hill & Volpe, 1981).

Status marmoratus involves necrosis, neuronal loss, hypermyelination and gliosis in the basal ganglia and thalamus. It is the least common of the neuropathologic models of hypoxic-ischemic encephalopathy. A combination of hypoxia and ischemia appears necessary to produce this lesion in animals (Volpe, 1987).

Systemic hypotension or global ischemia damages the vulnerable border zones of major cerebral arteries in the parasagittal supramedial aspects of the cerebral convexities. Parasagittal cerebral injury may involve infarction of the cerebrum and the underlying white matter along the vascular border zone. Neuronal necrosis of the parietal-occipital regions are typically more affected than anterior regions (Volpe, 1987).

Periventricular leucomalacia (PVL) is characterized by necrosis of the periventricular white matter that is adjacent to the external angles of the lateral ventricles and is associated with impaired vascular autoregulation and hypotension (i.e. ischemia). This pattern of injury is often documented in premature infants that survived at least the first week of life, and suffered cardiorespiratory insufficiency. Periventricular hemorrhage is a common complication that accompanies PVL (Volpe, 1987).

Focal or multifocal brain injury has multiple etiologies. Arterial or venous occlusion and cerebrovascular

insufficiency are common causes and may result in porencephaly, hydranencephaly or multicystic encephalomalacia (Hill & Volpe, 1981; Volpe,1987).

The localization of hypoxic damage is influenced by organogenesis defined as the structures undergoing active differentiation and organization (Towbin, 1971). Early in gestation, the deep structures undergo rapid development, whereas cortical structures organize as the third trimester progresses. The germinal matrix tissue is analogous to the tissue lining the neural tube, and diminishes and disintegrates from 30-40 weeks of gestation. Neuronal connections are formed in the periventricular germinal matrix region and then synaptic proliferation and myelination proceed in cortical structures (Perkins, 1987; Towbin, 1971). The deep cerebral veins are prominent in premature infants, whereas the dural sinuses are the primary source of venous drainage in the term infant. Following hypoxic-ischemic injury, venous drainage may be interfered with causing stasis-thrombosis and subsequent necrosis, infarction and phagocytosis of the surrounding tissue (Towbin, 1971; Volpe, 1987). As has been alluded to previously, there is a differential vulnerability of the developing brain to deficient oxygen supply. The type of brain injury is directly influenced by the gestational age of the developing organism. Post hypoxic-ischemic insult, premature infants typically present with damage to the deep, periventricular strata of the cerebrum (Towbin, 1971). The

fragile vascular bed around the ventricles receive a large portion of the blood perfusing the brain, and is prone to hemorrhage following abrupt alterations of cerebral blood flow and blood pressure. Therefore the elemental lesion, destruction of the periventricular region, would result from bleeding into the subependymal germinal matrix with subsequent rupture into the lateral ventricle. Secondary hydrocephalus, necrosis of adjacent white matter and neuronal destruction of the deep gray nuclei are often documented (Rorke, 1982; Volpe, 1989a). In contrast, the asphyxiated term infant demonstrates necrosis of the gray matter in the cerebrum as well as damage to the cerebellum and deep nuclei. Subdural hemorrhages, spinal cord and brain stem injuries are occasionally seen (Leech & Alvord, 1977; Rorke, 1982; Towbin, 1971). The differences in brain injury following asphyxia are attributed to the changing structure and energy demands of the developing nervous system, as well as the type of hypoxic-ischemic event(s) that each gestational age is likely to be exposed to (Volpe, 1987).

Experimental and human neuropathological studies suggest that the cochlear nuclei, superior olives, inferior colliculi (auditory relay nuclei), and the gracile and cuneate, ventrolateral thalamus, and parietal cortex (dorsal column-lemniscal pathway) are highly vulnerable to anoxic-ischemic insult, particularly in the maturing brain. As yet, the extent and ultimate prognosis of perinatal brain

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injury cannot be accurately determined early in life (Hill & Volpe, 1981).

CONSEQUENCES OF PERINATAL BRAIN INJURY

i.) Brain changes

The consequences of perinatal brain damage are dependent on the capacity of the central nervous system to reorganize at the time of insult. Following injury to the brain, there is direct tissue loss, as well as alterations in the growth and development of the brain. Normally, as the brain develops in utero, too many neurons are produced and therefore many appear programmed to die. After brain injury, this process is altered. Connections that are normally lost by axon retraction because of cell death, may persist following hypoxic-ischemic insult. However these multiple connections remain as immature synapses and may in turn disrupt the activity of undamaged areas (Janowsky & Finlay, 1986). Therefore brain injury appears to trigger the use of alternate pathways. The lesioned brain cells no longer compete for connections with other cells, and the adjacent spared areas may be recruited to recover the functions of the lesioned areas. This plasticity of the immature brain is usually at the expense of the functional abilities of the spared areas (Geshwind 1985).

Specific and predictable neuronal groups are selectively vulnerable to particular patterns of hypoxic-ischemic insult. The metabolic rates of neuronal structures appear to play a role in determining their vulnerability to

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diminished oxygen supply (Myers, 1975). For example, metabolically active tissues with tremendous blood flow requirements include specific nuclei of the brainstem, midbrain, basal ganglia and thalamus. Failure of fetal circulation would therefore preferentially damage these particular regions (Wigglesworth, 1984).

There is an emerging theory in the recent literature suggesting that neuronal groups are selectively vulnerable if the synapses contain large quantities of excitatory neurotransmitters such as glutamate. Following a deficient supply of oxygen to the brain, there appears to be an excessive release of toxic excitatory neurotransmitters. This hyperactivity of excitatory synapses may disrupt adjacent neurons, by causing destruction and reorganization. Many excitatory neuronal circuits mediate the control of normal movements, learning and thinking. Interestingly, survivors of selective neuronal necrosis following hypoxia often present with both behavioral and motor disturbances on follow-up (Johnston & Silverstein, 1986).

ii.)Neurodevelopmental sequelae

Perinatal brain damage may cause neurodevelopmental sequelae such as cerebral palsy, epilepsy, mental retardation, behavior, learning and communication disorders, sensory impairment, or minimal brain dysfunction (Graziani & Korberly, 1977; Rantakallio et al, 1987). The area of injury in the central nervous system will determine the

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subsequent deficit. Therefore one would expect visual problems associated with a lesion to the occipital lobe, intellectual and behavioral deficits with frontal lesions, and movement disorders such as dyskinesia documented following injury to the deep neuronal assemblies of the forebrain (Towbin, 1971).

Cerebral palsy (CP) is a group of disorders with varying pathogenesis and type of injury. This static encephalopathy is characterized by a disturbance of movement and posture due to injury to the central nervous system prenatally or early in the postnatal period. Approximately 50% have subnormal intelligence and 25% have a seizure disorder. Ambulation is usually affected and articulation may also be impaired (Paneth, 1986). Spastic diplegia, involving the lower extremities primarily, is typically seen in premature infants less than 36 weeks gestational age. This form of CP follows hemorrhage or ischemia in the germinal matrix with subsequent damage to the adjacent white matter. Fibers descending from the lower limb portion of the homunculus pass adjacent to the periventricular region that is vulnerable to ischemic injury, therefore the lower extremities are most likely to be affected. Asphyxia, traumatic injury or prenatal vascular insufficiency may cause spastic hemiplegia or spastic quadriplegia. The latter usually involves extensive deficits and mental retardation. Rare forms of cerebral palsy involving the extrapyramidal system (i.e. athetosis, dystonia) or

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cerebellum (ataxia) are likely due to hyperbilirubinemia, genetic or infectious causes (Perkins, 1987).

The major causes of mild to moderate developmental delay include genetic aberrations or sociocultural deprivation. Severe mental retardation implies significant hypoxic brain damage or cerebral dysgenesis (Naeye & Peters, 1987). The socioeconomic status and intellectual abilities of the parents will influence the degree of retardation in the child (Perkins, 1987).

Cerebral hypoxic lesions may be latent, and may be expressed as "soft signs" in childhood. Examples would include clumsiness and incoordination, behavioral disturbances such as hyperactivity, learning problems such as right/left confusion, and EEG irregularities. This concept of minimal brain dysfunction (MBD) was described extensively in the 50's and 60's and is now referred to as attention deficit disorder (ADD) (Towbin, 1971). Sixty cases with MBD were reviewed by Towbin (1971) and 4 types of damage were described: 1)subdural hemorrhage 2)mechanical injury of caudal structures (Spinal cord and brainstem) 3)hypoxic damage in premature infants 4) hypoxic damage in full term babies. The author suggests that genetic, metabolic, infectious and toxic processes may also contribute to MBD.

In summary, neonatal neuropathologic deficits can be expressed clinically as a variety of signs and symptoms of varying severity. Significant lesions resulting in CP or

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retardation are evident early in life whereas less devastating injury to the brain may only present itself later in childhood as ADD, or developmental deficits such as speech delay, incoordination, and problems with reasoning and perceptual skills. Microscopic deficits may not become clinically evident for many years (Moore, 1986).

Neuropathologic lesions are not fixed, but evolve over time both locally and distant to the lesion site. Early changes are biochemical (i.e. edema, pressure effects, altered membrane properties), structural (i.e. degeneration, sprouting), and physiological (i.e. decreased conduction and synapses, diminished feedback). Later changes are dependent on the age of the patient, type and extent of the lesion, and stimulation of the affected nervous system (Geshwind, 1985). Changes may be favorable, involving complete "recovery" of functional capacities. In the National Collaborative Perinatal Project, which involved follow-up of approximately 40,000 infants from more than 12 teaching hospitals, resolution of CP was observed in all children with monoparesis, in most with dyskinesia, ataxia or spastic diplegia, and in about 1/3 with hemiplegia or quadriplegia (Perkins, 1987). Therefore infants may survive an insult and appear to recover from functional losses as well. This has been attributed to neuroplasticity, the treatment advances in medicine, and the effects of rehabilitation in enhancing normal sensorimotor experiences (Moore, 1986). In fact, many of the children who "outgrew" CP had much higher

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rates of developmental deficits, particularly in speech and language, and visual/motor coordination. There is also an increased incidence of behavioral problems and seizure disorders in these children (Perkins, 1987).

PREDICTION OF OUTCOME

There is a vastly growing literature on prediction of outcome in newborns at risk for neurologic sequelae. Longitudinal studies have demonstrated that newborns at high risk include infants of very low birth weight (VLBW), newborns that are small for gestational age (SGA) and those with perinatal asphyxia. Other high risk groups include newborns presenting with neonatal seizures, a family history of neurologic disorder, cerebral hemorrhages or congenital malformations of the nervous system (Illingsworth, 1987; Kitchen et al, 1982; Nelson & Ellenberg, 1986; Perkins, 1987; Stewart et al, 1981).

Shapiro points out that "clinical predictions are never certain but are inherently probabilistic"[2], therefore the results from studies give an indication of the odds facing a child. High risk newborns are thus classified according to risk and this information is used at the discretion of the physician (Wasson et al, 1985; Shapiro, 1977). Prediction of outcome is important to clinicians for diagnosis, prognosis, and therapy. In other words, problems are identified as early as possible, and effective management is

the ultimate goal(Shapiro, 1977). Early recognition of infants at risk for neurodevelopmental sequelae enables the transdisciplinary medical team to 1) carefully re-evaluate and follow those at high risk 2) screen for associated problems 3) begin early therapeutic intervention and 4) effectively counsel parents regarding the prognosis of their child. Classification of patients by level of risk may further be useful in the design of clinical therapeutic trials. For example, the efficacy of physical or occupational therapy treatment approaches could be studied in groups of infants that are at relatively high risk for neuromotor delay (Ellenberg & Nelson, 1981; Shapiro, 1977).

Mathematical techniques in clinical prediction need not be complex. Two methods of analysis are favored; chi square analysis and multivariate techniques. The former involves cross tabulation of single variables (2 x 2 contingency tables) such as a neonatal test result and an outcome score on a developmental scale. Multivariate analysis examines the relationship between several variables at a time using multiple regression formulas (Ellison, 1984; Wasson et al, 1985)

One of the most devastating sequelae to the child, family and community would be CP and therefore much emphasis has been placed on the early recognition of this disorder of movement and posture. Early identification is strived for as early therapeutic interventions are thought to achieve maximal benefit (Bricker et al,1981; Ellenberg &

Nelson, 1981; Parette & Houcade, 1986; Scherzer et al,
1976). Reliable identification of CP early in infancy is
difficult (Ellenberg & Nelson, 1981) however severe deficits
are evident earlier (Ellison, 1984). Using multivariate
analysis of a large cohort, Nelson & Ellenberg (1986) have
determined that the pre and perinatal factors that best
predicted CP were maternal mental retardation, birthweights
of 2000 grams or lower, fetal malformation, and breech
presentation. Surprisingly, birth asphyxia, prematurity and
events during the delivery such as fetal distress were not
strongly associated with CP. Several difficulties in the
early diagnosis of CP can be enumerated. CP may be mild or
severe, and milder forms (i.e. brisk reflexes and mild
hypertonia) may only be identified at about 12-18 months of
age. Often, children "outgrow" tone abnormalities that are
characteristic of CP, and this may occur months or years
after the initial clinical presentation of the disorder.
Longitudinal studies have confirmed Nelson & Ellenberg's
initial findings that these transient neurologic
abnormalities that resolve are associated with a higher
incidence of speech defects, learning problems,
hyperactivity and mental retardation which manifest at
school age (Ellison, 1984). "The difficulties in the early
diagnosis, the impossibility of drawing the line between
normal and abnormal in some cases....and especially the
occasional disappearance of signs of cerebral palsy, make
it essential not to tell the mother about one's suspicions

until one is certain about the diagnosis and the permanence of the condition. Continued observation is essential in all but the severe cases"[3].

There is a tendency in follow-up studies of high risk newborns to focus on severe neurologic sequelae such as CP, however the majority of deficits are obvious only at school age, and may involve learning and behavioral problems and developmental deficits (Ellison, 1984). Neurologic examinations of the newborn, whether standardized (i.e. Brazelton, Prechtl, Einstein) or non-standardized, have been limited in their predictive value. Generally, neurologic signs that are worrisome include tone abnormalities, brain stem signs such as poor suck and swallow, and apathy (Brown et al, 1974; Donovan et al, 1962; Drillien, 1972; Ellenberg & Nelson, 1981). Nelson & Ellenberg (1979) found a 50 fold increased risk for CP in newborns with neonatal seizures or an Apgar score of 3 or less at 10 minutes. Furthermore, the predictive value of extensor hypertonia increases markedly when documented at 4 months of age. (Drillien, 1972; Nelson & Ellenberg, 1979). Abnormalities documented on examination of high risk children in the newborn period are nonspecific, and are related to the acute nature of the insult rather than the severity and longterm effects of the damage to the brain. The prognostic power of infant neurobehavioral assessments are further limited by maturational, environmental, physiological and psychosocial factors that influence the

clinical findings. Therefore initial clinical impressions may be erroneous and should not guide management decisions at present (Graziani & Korberly, 1977; Perkins, 1987). The predictive capacity should increase if a combination of clinical and diagnostic neurologic tests are utilized (Volpe, 1979).

Brain imaging techniques such as computed tomography (CT scan), ultrasound and magnetic resonance imaging have recently become available to patients in the neonatal intensive care unit (NICU), and are helpful in the early identification of significant brain damage such as cysts or atrophy (Paneth, 1986). Follow-up studies of high risk newborns that had CT scans in the neonatal period reveal that mild periventricular hypodensities which often resolve, or normal scans generally correlate with a favorable outcome. Severe periventricular leukomalacia (i.e. primarily seen in premature infants) and prominent cortical low density zones (suggested to be watershed infarctions or venous-stasis thrombosis seen typically in full term infants) are associated with abnormal development (Adsett et al, 1985; Lipper et al, 1986; Magilner & Wertheimer, 1980; Schrumpf et al, 1980). Morphologic changes detected on CT may resolve on serial testing and may in some cases reflect central nervous system (CNS) immaturity rather than resolving ischemic injury (Fitzhardinge et al, 1982). Furthermore, functional abnormalities in children may be clinically detected without

evidence of structural abnormality on CT. Therefore the interpretation and prognostic value of early CT findings must be considered with caution (Schrumpf et al, 1980). Sequential neurologic and neuroradiologic examinations over the first months of life would likely yield better correlations with outcome (Lipper et al, 1986).

Ultrasonographic studies are now being used extensively in the NICU to identify brain lesions. Ultrasound is an invaluable diagnostic tool for this population as it is portable, relatively inexpensive, and contains no ionizing radiation (Volpe, 1989b). Most ultrasound studies on premature infants have identified the degree of periventricular leukomalacia (PVL), which is defined as infarction of the white matter adjacent to the external angles of the lateral ventricles and is the neuropathologic correlate of spastic diplegia. Prior to routine neuroradiographic testing, these lesions were discovered only at autopsy (Bozynski et al, 1988; Calvert et al , 1986). The resolution of ultrasounds has improved markedly in recent years, therefore accurate identification of PVL is now feasible (Fawer et al, 1987). Prospective examination of preterm infants using cerebral ultrasound reveals that cysts associated with PVL appear at a mean postnatal age of 26 days. The vast majority of premature infants with PVL have abnormal motor development and other major developmental sequelae (Calvert et al, 1986; Fawer et al, 1987). Persistent hyperechogenic areas (diffuse or

extensive lesions typically), as well as cyst formation are associated with major motor and intellectual handicap particularly when appearing in frontal-parietal and frontal-parietal-occipital regions (De Vries et al, 1985; Fawer et al, 1985;Fawer et al, 1987; Volpe, 1989b). Isolated periventricular-intraventricular hemorrhages do not appear to be associated with a significantly increased risk of neurologic sequelae. In fact, post-hemorrhagic dilatation appears to be associated with a favorable outcome in many recent studies (Bozynski et al, 1988; De Vries et al, 1985; Fawer et al, 1985; Fitzhardinge et al, 1982). Therefore, serial brain ultrasonography appears to have an important role in prediction of outcome, particularly in preterm infants.

In summary, the outcome of perinatal brain injury appears to be related to the type, extent and location of the lesion, as well as to the neuroplasticity of the maturing nervous system. There are several reported studies showing recovery of apparently large lesions. However, children with cerebral lesions have a higher incidence of neurologic abnormalities later in life. The validity of imaging techniques as early predictors of permanent brain damage is disputed in the literature. Clearly, with improving resolution of brain morphology, as well as the use of sequential testing, the sensitivity and specificity of these tests are dramatically increasing. Magnetic resonance imaging may prove to be invaluable in the early recognition

of brain damage and several studies of this nature are likely underway. The extent of the neurologic deficit is presently difficult to accurately predict, particularly in children with mild to moderate developmental deficits. Furthermore, these tests cannot always assure a normal outcome (Bozynski et al, 1988; Fawer et al, 1985).

Brain imaging procedures provide some correlation with the child's developmental outcome, particularly when there is a clearcut structural deficit such as a cyst. Electrophysiologic measures have also been evaluated as possible indicators of longterm prognosis. A review of the literature on electroencephalographic (EEG) studies on high risk newborns demonstrates that this diagnostic tool is most predictive in extreme situations. Therefore a normal or immature pattern is associated with a good outcome whereas burst suppression or electrocerebral inactivity correlate with a poor prognosis. Epileptiform activity is a poor predictor of outcome (Holmes et al, 1982). Holmes et al (1982) determined in their study on asphyxiated infants that the EEG was more reliable in predicting outcome than the neonatal neurologic exam. Lacey et al (1986) found that EEG abnormalities documented in the first week of life in premature infants did not correlate with intracranial hemorrhage, severity of illness or neurodevelopmental outcome. Only the most abnormal records predicted a poor prognosis. Sarnat & Sarnat (1976) examined the relationship between EEGs and neurologic impairment in 21 full term

asphyxiated infants. Neonatal EEGs and clinical exams were classified into stages and analysis revealed that EEG findings paralleled clinical status. Furthermore, persistence of low voltage, theta and delta activity for more than one week, or isopotential EEGs were associated with death or neurologic sequelae. The changes on serial EEGs were more valuable than individual clinical signs on the neurologic exam.

EVOKED POTENTIALS AS A PROGNOSTIC TOOL: RATIONALE

Clinicians continue to search for more effective diagnostic tools that evaluate and monitor function in the nervous system. Using computer averaging techniques, evoked responses (or evoked potentials) are extracted from elec. ical activity picked up from electrodes placed on the scalp. Waveforms or potentials are generated from particular structures along the ascending sensory pathways. Surface recorded evoked responses have the tremendous advantage of being non-invasive, objective and reliable measures of brain function. Absolute and interwave latency measurements reflect central conduction time whereas amplitude ratios may be an index of synaptic activity. Evoked responses can be repeated in infancy to evaluate maturational changes characteristic of brain development. Serial testing may be of further value in documenting the evolution of brain injury (Chiappa, 1983; Gilmore, 1989; Laureau et al, 1988).

Evoked responses may prove to be invaluable as a prognostic tool in newborns at high risk for neurologic sequelae. Firstly, experimental and human neuropathologic studies have suggested that the ascending auditory and somatosensory relay nuclei are selectively vulnerable to hypoxic-ischemic injury, particularly in the maturing brain. For example, the cochlear nuclei, the superior olives and the inferior colliculi are often damaged following selective neuronal necrosis. The parietal cortex as well as thalamic and brainstem (i.e. gracile and cuneate nuclei) structures in the dorsal column medial lemniscal system are likely to be typically injured following partial or total asphyxia. Evoked potential studies on animals prior to and following hypoxia or ischemia have demonstrated that the responses are sensitive to alterations in oxygen availability. Changes in amplitude and latency have been noted in the auditory brainstem evoked response (ABR) and somatosensory evoked response (SER) following hypoxic-ischemic events, with a loss of components in extreme situations (Branston et al, 1984; McPherson et al, 1986; Sohmer et al, 1983).

In the recent literature, the prognostic value of evoked responses has been examined. Specific abnormalities in the ABR, such as prolonged central conduction time and abnormal V/I amplitude ratios, appear to predict later neurodevelopmental deficits, especially in asphyxiated full term infants (Hecox & Cone, 1981; Hrbek et al, 1977; Stockard et al, 1983). In a previous study (Majnemer,

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Master's thesis 1985; Majnemer et al, 1988), I examined the prognostic significance of the ABR in high risk newborns. An abnormal ABR, which included increased I-III or I-V interwave latencies, abnormal V/I amplitude ratios (< 0.5) or abnormal dispersal ratios (< 0.2), predicted neurologic deficits at 1 year of age. However, a normal ABR did not ensure a normal outcome. ABR findings reflect brainstem function from the eighth cranial nerve to the midbrain, but does not evaluate conduction along higher centers of the nervous system, therefore limiting the applicability of this test in determining extent of damage to structures rostral to the inferior colliculi. However, this study has delineated the high specificity and positive predictive power of the ABR in a high risk population from the NICU. The ABR abnormalities appear to reflect one type of pathology, selective neuronal necrosis, which involves brainstem structures as well as vulnerable structures in the cerebellum, thalamus and cortex (Majnemer et al, 1988; Volpe, 1987).

Due to the limitations of the ABR as a prognostic indicator of brain injury, I propose to evaluate the possible additional value of using the SER in conjunction with the ABR in high risk neonates. The SER assesses the integrity of the ascending sensory projections from the periphery to the somatosensory cortex, and therefore a wider distribution of the central nervous system would be probed. The ABR and SER will be recorded simultaneously on a new

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cohort of both healthy and high risk newborns, so that the predictive value of these two sensitive electrophysiologic tests may be statistically determined.

OBJECTIVES OF THIS STUDY

1. To establish normative data for SERs in healthy full term as well as low risk premature newborns tested at 40 weeks conceptional age.

2. To describe the maturational changes that occur in SER recordings over the first 6 months (corrected age).

3. To compare SER recordings in normal and high risk newborns and determine whether or not this test can distinguish the two groups.

4. To assess the prognostic significance of multi-modality evoked responses in a group of newborns at high risk for neurodevelopmental sequelae.

In Chapter 1 (i.e. article 1), maturational changes in the SER were studied and described in a group of 18 healthy full term newborns. These infants were tested in the first week of life, and testing was repeated at 2-3 months and 6-7 months of age. A reliable technique for generating reproducible SERs in neonates is delineated and the effects of age, filter settings and state of consciousness are described (objectives 1 and 2).

In Chapter 2, an ABR and SER were performed on a group of low risk premature infants at term (40 weeks conceptional age). Results were compared with those of the healthy full term group, so that the possible maturational effects of early exposure to extrauterine environment could be investigated. If there is no significant difference in evoked response measurements between the 2 groups (full term and premature) when tested at the same conceptional age, one could conclude that the nervous system myelinates at a similar rate. Therefore it would be feasible to use normative data derived from a healthy full term population for high risk premature infants that are tested at term (objective 1).

SER findings in 34 high risk newborns are described in Chapter 3. The type and the evolution of these electrophysiologic abnormalities are presented and their relationship with developmental status in infancy is explored.

The prognostic significance of multi-modality evoked responses in high risk newborns is reported in Chapter 4. The predictive value of two evoked response tests (ABR and SER) are examined individually and in combination and the clinical utility of the findings is highlighted.

A Discussion follows the four chapters and summarizes the literature on SER in healthy and high risk newborns. The rationale for using evoked responses as a prognostic tool

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are delineated, and the reported studies describing the prognostic value of each modality of evoked response testing in graduates of the NICU are summarized. The results of my research are highlighted in context with the existing literature.

Finally the study rationale and clinical relevance are re-emphasized in the <u>Conclusions</u>. Original contributions of this prospective study are enumerated as well.

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FOOTNOTES

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NOTE TO THE READER REGARDING MANUSCRIPTS:

With the exception of the first article, which was a collaborative effort between Dr. E. Laureau and myself, I was solely responsible for selecting an appropriate experimental design, organizing/implementing all testing procedures, as well as carrying out statistical analysis and manuscript preparation for the studies that follow.

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A longitudinal study of short latency somatosensory evoked responses in healthy newborns and infants [1]

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Summary   Maturational changes in short latency somatosensory evoked responses (SERs) were studied in 18 healthy full-term newborns in the first week of life and consequently repeated at 2–3 and 6–7 months of age. Both median nerves were electrically stimulated individually and evoked responses were recorded at 3 levels: Erb's point (EP), second cervical vertebra (CII), and contralateral parietal scalp (C'c). In the neonatal period, results of 32 stimulated nerves were obtained in all cases at the EP and CII levels. At the parietal level, potentials were present in 85% of cases, absent in 9% and questionable in 6%. Parietal potentials were occasionally noted on one side only. Repeat examinations at 2–3 and 6–7 months of age demonstrated significant maturational changes in the SERs. These changes were most prominent in the neonatal period and 2 months of age. They included decreased interpeak latencies, increased amplitude and markedly diminished dispersion of parietal potentials. Minimal changes in wave form configuration and latency were noted at the EP and CII level. These findings most likely reflect myelination and increased synaptic efficiency predominantly in the central sensory pathway. The purpose of this investigation was to delineate a reliable technique for SERs in newborns and infants that could be applied both to research and clinical settings. Normative data were established in newborns and infants as this will help us in accurately differentiating a normal from an abnormal group of neonates and infants.

Key words: Somatosensory evoked response; Newborn; Infant; Maturation

The clinical usefulness of somatosensory evoked responses (SERs) has been widely recognized in the literature (Mastaglia et al. 1978; Anziska and Cracco 1980; Oh 1980; Chiappa and Ropper 1982; Mauguière et al. 1982) in adults. In the neonatal period and in childhood, this technique is difficult and special procedures are necessary to perform this test. Maturational changes of somatosensory pathways were assessed for the upper limbs in

several studies (Hrbek et al. 1968; Desmedt and Manil 1970; Blair 1971; Hrbek et al. 1973; Cullity et al. 1976; Desmedt et al. 1976; Laget et al. 1976. Pratt et al. 1981; Hashimoto et al. 1983; Pallotta et al. 1984; Willis et al. 1984; Cadilhac et al. 1985, Sitzoglou and Fotiou 1985). Some authors studied long latency SERs (Hrbek et al. 1973; Cullity et al. 1976; Laget et al. 1976), others examined only short latency SERs (Desmedt et al. 1976; Hashimoto et al. 1983; Willis et al. 1984) that are less affected by state of consciousness. Few authors reported findings of both peripheral and central responses (Pratt et al. 1981, Willis et al. 1984; Sitzoglou and Fotiou 1985). All these studies utilized cross-sectional data. Results were highly discrepant and could not be easily applied clinically. Comparisons between studies are difficult because of different stimulating and recording parameters (stimulated nerves, type of stimulus,

rate, montage, filters) that could alter the latencies and the morphology of the wave forms (Celesia 1985). Therefore, our objectives were:

(1) to establish a technique that was easy to apply to both clinical and research settings, particularly in the neonatal period;

(2) to provide an objective method of measuring the wave forms both in peripheral and central somatosensory pathways;

(3) to assess the maturational changes in the short latency SER in a longitudinal study, in a cohort of healthy newborns.

Material and methods

(I) Subjects

Eighteen healthy newborns from a well baby nursery were chosen with the following selection criteria: Apgar score >7 at 5 min; birth weight appropriate for gestational age (>3rd percentile); gestational age between 37 and 42 weeks; without perinatal complications.

Serial testing was carried out to assess maturational changes of the SER in infancy. They were tested in the neonatal period (between the 2nd and the 4th day after birth), at 2–3 months and at 6–7 months conceptional age (defined as gestational age plus chronological age).

(II) Methodology

(a) Recording technique. SERs were performed after or during feeding, therefore the subjects were quiet or asleep. At each recording, the different states of consciousness (1, alert-restless; 2, alert calm; 3, drowsy; 4, asleep) were noted. The Grass model 10 ER system was used with G2 negativity yielding an upward deflection. Both median nerves were stimulated separately. Electrical square wave pulses (0.2 msec duration) were delivered by means of a special infant stimulator (DISA) that was applied at the wrist level, at a rate of 4/sec with an intensity sufficient to obtain a minimal thumb twitch. Electrical activity was picked up by gold cup surface electrodes applied with paste on the skin and resistance was maintained below 5 kΩ. Surface electrodes were placed at the following levels: at Erb's point (EP), at the second cervical

vertebra and at the contralateral parietal level (at C′3 or C′4: 2 cm behind C3 or C4 as defined by the 10-20 international system). The ground was placed on the upper limbs. Arm length was measured from the stimulation site to the EP electrode. The first 3 derivations (FPz-EP, FPz-CII, FPz-C′c) were filtered at 30–3000 Hz whereas the 4th derivation (FPz-C′c) was filtered at 3–3000 Hz. The response was amplified 100,000 × with a vertical scale ×4. The sweep was set at 50 msec with a 1.5 msec delay. At least 2 series of 512 sweeps were recorded to ensure reproducibility of the wave forms and were superimposed on the X-Y plotter.

(b) Wave form analysis. Absolute latencies were measured from the onset of the stimulus to the peak. In the neonatal period, the EP wave form often had a V-shape morphology with 2 negative peaks. For measurement of latency, the second negative peak was always taken, regardless of amplitude. If there was a single prominent negative peak, it was measured for EP latency. At the CII level, if there was a single prominent peak, it was measured for CII latency. If the peak was bifid, the second peak was taken. If CII was somewhat dispersed, the last point before the drop-off was taken. At the parietal level, if the peak was clearly visualized, latency was measured at the peak. If not, the point where the wave form begins to rise from the baseline and the corresponding trough (P22) were indicated. N19 peak could be estimated by the intersection of the rising and descending slopes. When P22 was difficult to identify, the point at which the wave form returns to baseline was labeled as P22.

The interpeak latencies (IPLs) EP-N13, N13-N19 and N19-P22 were calculated. Furthermore, the amplitude of N13 relative to N19 was calculated (N13/N19), the amplitude being defined as the height from peak to trough of each wave. As the 2 recordings were superimposed, an average of the two was derived (Fig. 1). Dispersal of the parietal potential was defined as the height over the base of this wave. Dispersed wave forms are typically of low amplitude (height) and broad based (base), therefore this would yield a low ratio. Well defined peaks are of high amplitude and of shorter duration therefore yielding a high
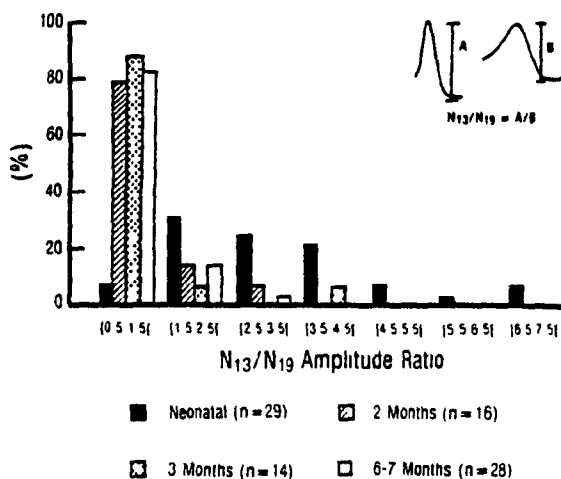
Fig. 1. A comparison of the amplitude of N13 relative to N19. In the neonatal period, N19 was attenuated, therefore, the amplitude ratio was large. During infancy, N19 grew in size, therefore, the amplitude ratio decreased.

ratio value. The base was defined as the duration of the wave form, from the positive peak before N19, to the return to baseline or trough (P22). The height of the wave form was from the highest to the lowest point within the limitations of the baseline (Fig. 2).
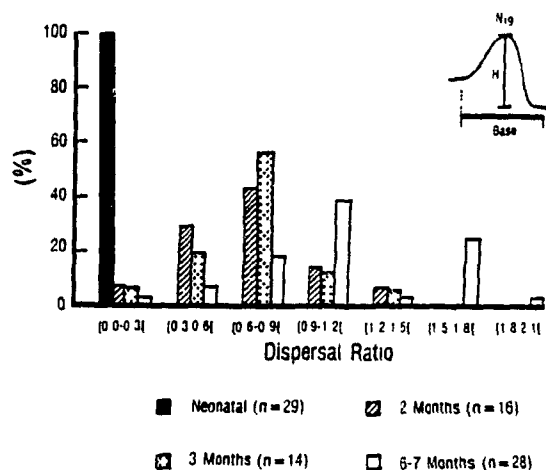

Fig. 2. The amplitude of N19 relative to its base (dispersal ratio). In the neonatal period, N19 was of very low amplitude and dispersed and therefore, the dispersal ratio was small. During infancy, the height of N19 increased and its base decreased, therefore, the dispersal ratio increased as a function of age.

(c) Statistical analysis The evolution of latencies and interpeak latencies, amplitude ratios and dispersal as a function of time was analysed by ANOVA for repeated measures. The Scheffe post-hoc test was used for comparisons of means over time.

Results

(I) Sample

In the neonatal period, 18 children were recorded (13 males and 5 females, Table I). The children were all asleep during the test. Thirty-three median nerves were stimulated; for one median nerve, parietal potentials could not be recorded because of electrical artifact

During infancy, 13/18 parents agreed to come for follow-up testing. Children were retested at 2 or 3 months and at 6 or 7 months of age. Four parents agreed to have their children retested 3 times so that additional data points could be acquired. Results at 2–7 months that were recorded during state 4 were eliminated from the study. At 2 and 3 months of age, 7 and 8 children were respectively recorded. Latencies and interpeak latencies (IPLs) were not pooled between 2 and 3 months of age because significant differences were found for some parameters between these 2 age groups (Tables II and III) At 6 and 7 months of age, 8 and 7 children were respectively recorded. Latencies and IPLs were pooled between 6 and 7 months of age.

(II) Maturational changes

(a) Morphological changes. In the neonatal period, at the EP and CII level, the potentials were easily recognizable and always present. The EP wave form often had a V-shape morphology with 2 negative peaks. The N13 wave form was a negative prominent peak, sometimes bifid or dispersed. At the parietal level, the negative peak (N19) and following positive peak (P22) were of low amplitude and dispersed when compared to EP and N13. In 32 stimulated nerves, 27 parietal potentials were present (85%), 2 were questionable (6%) and 3 were absent (9%) (Fig. 3). In the questionable recordings, there is a clearly repro-

TABLE I

Main characteristics of the cohort studied in the neonatal period and during infancy.

	Neonatal period	2 months	3 months	6 months	7 months
Children (no)	18	7	8	8	7
Conceptional age (CA in weeks)	37–42	47–48	51–55	63–66	67–69
Mean CA + 1 S D	39 3 + 1.4	47 6 + 0.5	52.4 + 1.2	64.1 + 1	68 + 0.6
Stimulated nerves (no)	33	14	16	16	12

TABLE II

Mean values (M) and standard deviations (S D) in msec of SER peak latencies in healthy newborns and infants. N, number of subjects M > M' indicates a statistically significant difference between the means of the 2 groups (P < 0.05). M1, mean of latency at the neonatal period; M2, mean at 2 months; M3, mean at 3 months; M4, mean at 6–7 months.

		Neonatal period (1)	2 months (2)	3 months (3)	6–7 months (4)	Significant differences between groups 1–4
EP latency	M	6 32	6.00	5.97	5.34	
	S.D	0.73	0.55	0.59	0.43	M1 > M4, M2 > M4
	N	33	14	16	28	
N13 latency	M	9 98	8.96	8.56	7 71	
	S.D	0 72	0.54	0.40	0.55	M1 > M2, M1 > M3, M1 > M4
	N	33	14	16	28	
N19 latency	M	25.00	20.39	19 16	17 52	M1 > M2 M1 > M3, M1 > M4,
	S.D.	2.91	1.16	1.09	0.79	M2 > M4
	N	29	14	16	28	
P22 latency	M	34 79	28.50	26.81	23.62	M1 > M2, M1 > M3, M1 > M4,
	S D	4 03	1.22	2.02	1.04	M2 > M4, M2 > M3
	N	29	14	16	28	

TABLE III

Mean value (M) and standard deviations (S.D) in msec of SER interpeak latencies in healthy newborns and infants. N, number of subjects M > M' indicates a statistically significant difference between the means of the 2 groups (P < 0.05) M1, mean of IPLs at the neonatal period; M2, mean at 2 months; M3, mean at 3 months; M4, mean at 6–7 months.

		Neonatal period (1)	2 months (2)	3 months (3)	6–7 months (4)	Significant differences between groups 1–4
EP-N13	M	3.67	2.96	2.59	2.37	
	S.D.	0.61	0 66	0.42	0.50	M1 > M2, M1 > M3, M1 > M4
	N	33	14	16	28	
N13-N19	M	15 10	11.43	10 59	9.77	M1 > M2, M1 > M3, M1 > M4,
	S.D.	2.68	1.03	0.84	0.98	M2 > M4
	N	29	14	16	28	
N19-P22	M	9.83	8.11	7 66	5.58	
	S.D.	3.02	0.59	1.48	0 93	M1 > M2, M1 > M3, M1 > M4
	N	29	14	16	28	

ducible rise from baseline, however, the wave form is of low amplitude and dispersed, with a voltage of the N19-P22 wave less than 0.22 μV. Every child had a clearly recognizable potential on at least one side. No child had absent and/or questionable potentials on both sides. The conceptional age (CA) of children with questionable or absent parietal potentials varied from 37 to 40 weeks.

At 2, 3 and 6–7 months of age, minimal morphological changes were observed at the EP and cervical levels. When compared to the neonatal period, the shape of the wave forms was similar and the amplitude of potentials increased slightly. At the parietal level, however, major morphological changes were observed. The amplitude of the N19-P22 wave increased markedly and the duration of the wave form decreased. Parietal potentials were present in all cases. Four out of the 5 children with absent or questionable parietal potentials in the newborn period were retested at 2–3 months and all four had clearly recognizable wave forms. At 2–3 months of age, a second negative peak following P22 could generally be observed (Fig. 4).

(b) Latencies and interpeak latencies. The major effect of time was a decrease in latencies

and IPLs at the 3 anatomic levels (at least $P < 0.05$, Tables II and III). There was no significant difference between left and right arm Except for the EP latency, all mean values were significantly higher in the neonatal period than at 2, 3 and 6–7 months, respectively. The mean EP latency was significantly decreased (at least, $P < 0.05$) only at 6–7 months of age. N13, EP-N13 and N19-P22 did not change significantly after 2 months In contrast, N19, P22 and N13-N19 showed significant maturational changes over time between 2 and 7 months (at least, $P < 0.05$)

Arm length was found to be negatively correlated to N13, N19, P22, EP-N13, N13-N19 ($r = -0.70$ to -0.85) For EP and N19-P22, coefficients of correlations were only -0.44 and -0.58 respectively ($P = 0.0000$).

The variations of N13-N19 IPLs as a function of conceptional age are illustrated in Fig. 5 Most infants were recorded 3 or 4 times, few were recorded only once. With increasing conceptional age, all IPLs as well as data variability decreased with increasing conceptional age.

(c) Amplitude ratio (N13/N19) and dispersal ratio of N19 In the neonatal period, the mean value of N13/N19 was 3 19. This ratio decreased significantly at 2 months of age (1.30, $P < 0.05$)
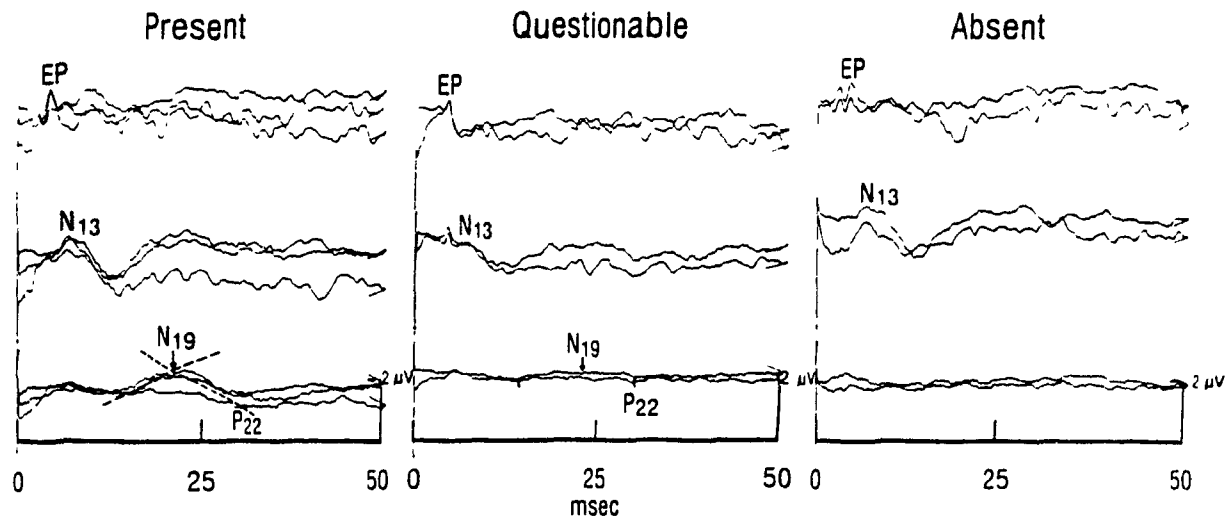

Fig. 3. Wave form identification of N19 in the neonatal SER. On the left, parietal potentials are present In the center, N19 and P22 are defined as questionable: there is a slight increase of the baseline, no more than 0.22 μV, and potentials are very dispersed On the right, there are no cortical potentials.
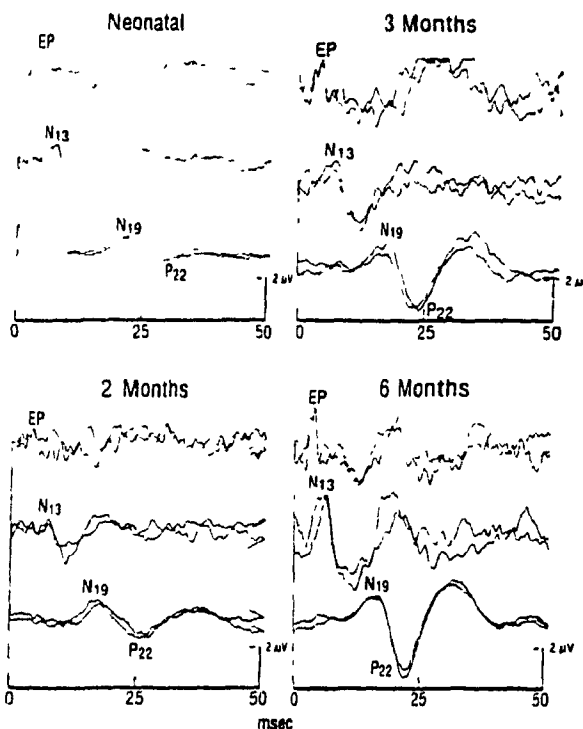
Fig. 4. A longitudinal study of SERs of the right median nerve in one child at 0, 2, 3 and 6 months of age

Fig. 5. The variations of N13-N19 IPLs as a function of conceptional age

and did not change thereafter (Table IV and Fig. 1).

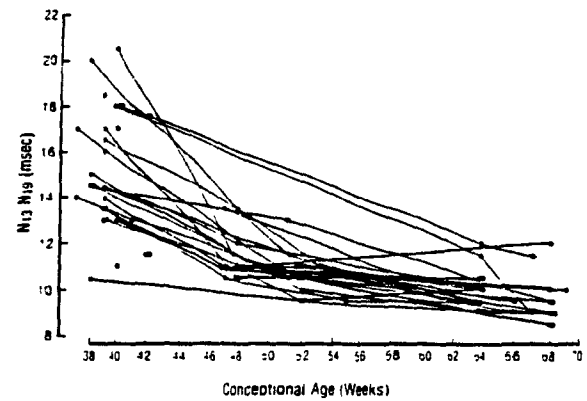The mean dispersal ratio of N19 was 0.16 in the newborns and increased markedly at 2 months (0.71, $P < 0.05$). Again, no further change was noted between 2 and 6–7 months (Table IV and Fig. 2).

(d) Effect of filter settings. The parietal potentials were recorded using 2 types of filter settings: 30–3000 Hz and 3–3000 Hz. The effect of raising the low cut-off filter was most evident in the neonatal period as can be seen in Fig. 6. Using 3–3000 Hz filter setting, the parietal potential appeared as a large negative wave without a falling slope in the majority of recordings. With 30–3000 Hz, N19 was shifted to the left in all cases and P22 (i.e., trough or return to baseline) was recognizable. During infancy, the discrepancy was not so marked, parietal potentials were clearly identifiable using both types of filter settings.

TABLE IV

Mean values (M), minimum and maximum of amplitude ratios N13/N19 and dispersal ratios of N19 in healthy newborns and infants. N, number of subjects. M > M' indicates a statistically significant difference between the means of the 2 groups ($P < 0.05$). M1, mean of ratios or dispersal at the neonatal period; M2, mean at 2 months; M3, mean at 3 months; M4, mean at 6–7 months.

		Neonatal period (1)	2 months (2)	3 months (3)	6–7 months (4)	Significant differences between groups 1–4
N13/N19	M	3 19	1.30	1 31	1.14	
	Min	0.86	0.52	0 64	0 50	M1 > M2, M1 > M3, M1 > M4
	Max	7.25	3.43	3.67	3.00	
	No	29	14	16	28	
Dispersal	M	0.16	0.71	0.71	1.10	
	Min	0.05	0.20	0.20	0 19	M1 > M2, M1 > M3, M1 > M4
	Max	0.28	1.48	1.38	1.92	
	No	29	14	16	28	

EP

N₁₃

N₁₉   30-3000 Hz

P₂₂

3-3000 Hz

2 µV

0   25   50 msec
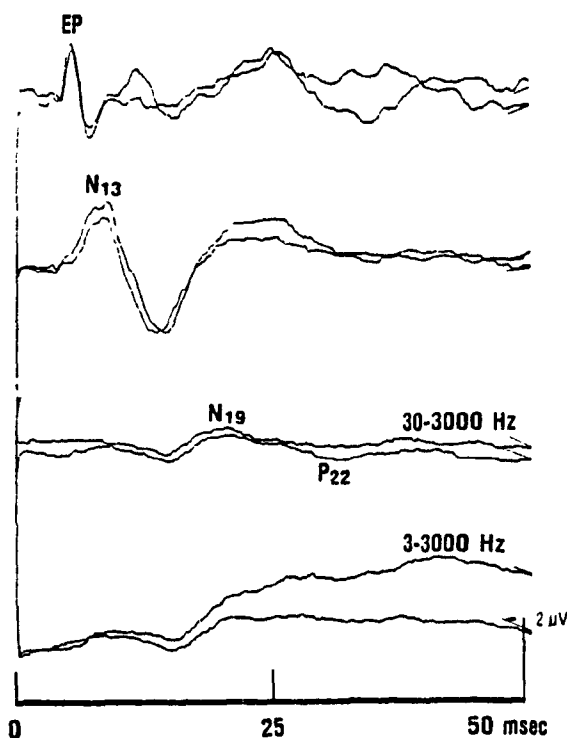
Fig. 6. The effect of filter settings in the neonatal period.

FPz-C'c

N₁₉   Case 1

Awake

Asleep

P₂₂

N₁₉   Case 2

Awake   P₂₂

Asleep   2 µV

N₁₉   P₂₂
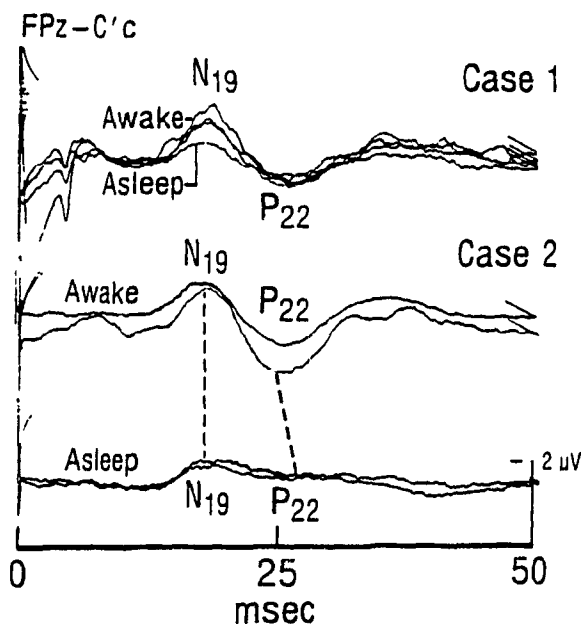
0   25   50
msec

Fig. 7. The effect of state on SERs. Case 1 demonstrates a decrease in amplitude of N19 whereas case 2 also demonstrates a slight increase of P22 latency.

However, a slight shift to the right and a greater amplitude in parietal potentials were observed at 3-3000 Hz when compared to 30-3000 Hz

(e) Effect of state. In the neonatal period, all the newborns were asleep during the procedure During all follow-up testing, most of the children were recorded awake. Some of them were recorded awake and then asleep during the same test Differences were noted in SER results N19, P22 amplitude decreased during sleep and P22 latency tended to increase (Fig. 7).

Discussion

We have tried to establish the optimal technique for SERs that was reliable and easy to reproduce in order to generate normative data useful for clinical and research applications, particularly in the neonatal period Generally, SERs in newborns are performed by electrical stimulation of the median nerve at the wrist (Blair 1971, Hrbek et al. 1973; Cullity et al. 1976, Laget et al 1976; Hashimoto et al. 1983, Willis et al 1984, Cadilhac et al. 1985; Sitzoglou and Fotiou 1985) This technique is simple and the intensity is adjusted to produce a minimal thumb twitch Hrbek et al. (1968) and Pratt et al. (1981) used mechanical stimulation whereas Desmedt et al. (1976) used electrical stimulation of the fingers. These techniques are more difficult as one is not certain whether the nerve is being stimulated A thumb twitch ensures that the median nerve is in fact stimulated. The rate of stimulation used was 4/sec This was done in order to diminish the time of recording. We used surface electrodes as they were easy to apply and non-invasive. Recording electrodes were placed at different levels in order to assess the maturational changes of both peripheral and central lemniscal pathways. This montage was used by Pratt et al. (1981), Willis et al. (1984) and Sitzoglou and Fotiou (1985) Amplifier filter settings have varied widely in the literature Cullity et al. (1976) used 2-300 Hz and Hashimoto et al 1983) used 50-3000 Hz. Desmedt et al (1974) recommended widely open filters Like Willis et al. (1984), we used 2 kinds of filter for parietal derivations so that we could determine the opti-

mal filter setting in the neonatal period (30–3000 Hz). The discrepancy between the 2 filter settings was noted principally in the neonatal period.

We have studied short latency responses (with a sweep time of 50 msec) because they are the most reproducible components of the SER although they are somewhat affected by sleep state (Hrbek et al. 1969; Desmedt and Manil 1970; Hashimoto et al. 1983) In this study, we have attempted to control for the effects of state of consciousness on the parietal potentials. Newborns were tested when drowsy or asleep as this is their predominant state. In contrast, infants were never recorded asleep as this was found to induce a decrease in amplitude of N19-P22 wave (Hrbek et al. 1969) and an increase in latency of P22 (Desmedt and Manil 1970; Hashimoto et al. 1983).

Previous authors did not specify the percentage of parietal potentials in the newborn period. In a study of SERs in 34 sleeping newborns, Blair (1971) obtained parietal potentials only in half of them. Pratt et al. (1981) obtained a parietal potential in 1 out of 10 newborns but used mechanical stimulation of the fingers. The most comparable study to ours is that of Willis et al. (1984). They were able to obtain EP and parietal potentials in only 2/3 of cases. In our study, we obtained EP and cervical potentials in all cases. At the parietal level, we obtained a potential in 85% of cases in the neonatal period.

The use of absolute amplitudes is limited because of their extreme variability (Chiappa and Ropper 1982). Relative amplitudes between N13 and N19 and dispersal ratios of N19 were established. They are useful to assess more objectively the amplitude and dispersion of wave form components. This study demonstrates dramatic changes in amplitude ratios (N13/N19) and dispersal of N19 from the neonatal period to 2 months of age reflecting significant maturational changes in the parietal potential.

SERs are useful to assess the maturation of the peripheral and central lemniscal pathways. The EP potential is thought to be generated by fibers of the brachial plexus and N13 is felt to be generated by dorsal column nuclei (Chiappa and Ropper 1982) and/or brain-stem lemniscal pathways (Anziska and Cracco 1981). EP and N13

both allow the assessment of peripheral pathways. N19, whose origin is more controversial, is generated either in the thalamus (Chiappa et al. 1980; Chiappa and Ropper 1982) or in the sensory parietal cortex (Desmedt and Cheron 1980). P22 is thought to originate in the parietal cortex. N19 and P22 can be used as indices of central maturation of lemniscal pathways. In the neonatal period, the peripheral lemniscal pathways seem more mature than the central ones. EP and N13 were recorded in all children and their waves were clearly recognizable. On the contrary, parietal potentials were of low amplitude and dispersed and only 85% could be recorded. The marked variability of the N13-N19 interpeak latency in the neonate may correspond to the biologic variation in myelin deposition as demonstrated anatomically by Gilles et al. (1983). The maturational changes of SERs were shown by repeat examinations at 2, 3 and 6–7 months of age. The more impressive changes for both peripheral and central lemniscal pathways were between the neonatal period and 2 months of age. Minimal changes in wave form morphology and latency were noted at the EP and CII levels. This presumably reflects the opposing factors of increasing arm length and increasing conduction velocity and the fact that peripheral sensory pathways seem more mature than central sensory pathways (Yakovlev and Lecours 1967). In contrast, changes were more marked in central pathways, including decreasing latencies, IPLs, increasing amplitudes and markedly diminishing dispersion of parietal potentials. These findings most likely reflect myelination and increased synaptic efficiency predominantly in the central sensory pathways.

We are presently investigating the usefulness of early SER testing in high risk newborns. Preliminary findings suggest that healthy and high risk newborns can be differentiated by early SERs. Furthermore, SER abnormalities may reflect the extent and evolution of anoxic-ischemic injury and may therefore have predictive value (Majnemer et al. 1987) . This subject is part of an ongoing prospective study in our laboratory.

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THE EFFECT OF GESTATIONAL AGE AT BIRTH ON SOMATOSENSORY

EVOKED POTENTIALS PERFORMED AT TERM

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ABSTRACT

Multi-modality evoked potentials are widely used in newborns to assess the maturation and integrity of the sensory pathways. Reliable normative data are needed to maximize the utility of this technique as a diagnostic and research tool. Several electrophysiologic studies on the maturational changes of the ABR have demonstrated that latency measurements decrease as a function of increasing conceptional age, however maturational studies of the somatosensory evoked potential particularly in low risk premature infants are limited. The existing evoked potential literature in healthy newborns proposes that maturation of the central nervous system occurs at a predictable rate irrespective of a given gestational age at birth. Behavioral studies of premature infants suggest that neurologic development may be altered by early extrauterine exposure. The purpose of this study was to determine whether auditory brainstem or somatosensory evoked potential conduction times were comparable in premature and full term infants matched for conceptional age. The results of this study suggest that myelination is determined by conceptional age, independent of premature birth.

KEY WORDS: auditory brainstem evoked potential- somatosensory evoked potential- conceptional age- premature- full term- myelination

INTRODUCTION

Recent longitudinal studies determining the developmental outcome of high risk newborns have uniformly demonstrated that the chances of healthy survival has dramatically increased over the past two decades. However, the handicap rate for neonatal intensive care unit graduates has remained stable (1-2). Therefore objective tests are needed to assess the structure and function of the immature brain, and monitor neurologic maturation, so that neonates at-risk for developmental handicap may be identified early and managed effectively.

Auditory, visual and somatosensory evoked potentials are widely advocated for neurologic and audiologic assessment of asphyxiated and other high risk newborns (3-4). Evoked potentials may be used as an objective indicator of maturation of the central nervous system and this electrophysiologic technique is of further value as a research tool. Reliable normative data must first be established so that the utility of this diagnostic technique may be fully realized (3-5).

There is a conflicting body of knowledge in the literature regarding the neurologic maturation of infants in the intrauterine versus the extrauterine environment. One view stipulates that the brain develops (e.g. myelinates) independent of the environment. This has been demonstrated by electrophysiologic and histopathologic studies of the nervous system (3-6). Several studies support the view that

neurologic development in pre-term newborns is accelerated with intrauterine distress and subsequent early extrauterine exposure. The latter view is reinforced by behavioral methods of assessment primarily (3,7,8). It is well established that latency measurements in auditory brainstem evoked potentials decrease as a function of conceptional age (defined as gestational age plus postnatal age), and appears to reflect maturation of the nervous system early in life (5,9,10). Therefore developmental changes in central conduction time are independent of the environment of the infant. Normative data for somatosensory evoked potentials in newborns are limited, particularly for premature infants (3,11-13).

The aim of this study was to determine whether or not low risk premature infants tested at term (40 weeks conceptional age) demonstrate comparable auditory brainstem and somatosensory evoked potentials as healthy full term infants tested in the first week of life. Alternatively, the effects of chronological age on the evoked potentials in premature and full term infants were examined as well.

METHODS

I. SUBJECTS

Healthy full term newborns (gestational age > 3 6 weeks) were obtained from a well baby nursery. Selection

criteria included an Apgar score of 8-10 at 5 minutes, a birthweight appropriate for gestational age and without evidence of pre or perinatal complications. This group was part of a cohort of healthy and high risk newborns being followed longitudinally so that the predictive value of multi-modality evoked potentials may be delineated (12,14). Low risk premature infants were selected from the premature nursery of the Royal Victoria Hospital. Criteria for admission to the study included an Apgar of 8-10 at 5 minutes and oxygen by mask for less than 2 minutes at delivery, gestational age < 37 weeks, birthweight > 1500 grams and appropriate for gestational age, and no evidence of pre or perinatal complications. Therefore infants with evidence of fetal distress or asphyxia at delivery, birth trauma, congenital anomalies, neurologic abnormalities, sepsis, meningitis, respiratory difficulties or metabolic problems were excluded. This study has been reviewed by an ethics committee. Informed consent was obtained for all subjects.

II. EVOKED POTENTIAL TESTING

All evoked potential testing was carried out in the Evoked Potentials Laboratory of the Montreal Children's Hospital. The same recording techniques and standards for measurement were used for the full term and premature infants. Full term infants were tested in the first week of life and were reassessed at 2-3 months and 6-7 months as

part of a longitudinal study (12). For this study, premature infants were tested as close as possible to 40 weeks conceptional age.

auditory brainstem evoked potentials-
Gold cup electrodes were pasted to the vertex (Cz) and each earlobe (A1-left ear, A2-right ear) and a ground was placed on the forehead. Positivity at the vertex produced an upward deflection. With the earphone resting gently on the pinna, monaural rarefaction click stimuli were presented at a rate of 11/sec to each ear at 70 decibels hearing level (dBHL). At decreasing intensities at a rate of 31/sec, threshold was established. Filters were set at 100-3000 Hz and input was amplified 100,000X. One thousand and twenty four responses were averaged per trial, and at least 2 trials were carried out at each intensity to ensure reproducibility of the waveforms. Averaged responses were printed on an x-y plotter.

somatosensory evoked potentials-
Gold cup electrodes were applied with electrode paste to Erb's Point (EP), over the second cervical vertebra (CII) and 2 centimeters behind C3 and C4 (as defined by the 10-20 system); electrodes were referenced to Fz. Negativity at the EP, CII, C3 and C4 produced an upward deflection. Newborns generally were drowsy or asleep throughout testing. An electrical square wave pulse was delivered to each median nerve using an infant stimulating electrode at a rate of 4

Hz and a duration of 200 usec, and an intensity sufficient to produce a minimal thumb twitch. Filters were set at 30-3000 Hz and input was amplified 100,000 X. Five hundred and twelve responses were averaged per trial, and at least 2 trials were recorded to ensure waveform reproducibility. Two trials were superimposed on an x-y plotter.

Absolute and interwave latencies were measured by 2 independent readers (AM and BR). Means and standard deviations were derived for both full term and premature infants tested at approximately 40 weeks conceptional age. Measurements were further determined for full term infants at < 1 week and at approximately 8 weeks (i.e. 2 months) chronological age (weeks after birth) and for premature infants at 6-8 weeks chronological age. Therefore the effects of intrauterine versus extrauterine environment could be explored.

RESULTS

Evoked potentials were carried out on full term infants in the first week of life (day 1-3) whereas premature infants were tested between 3-8 weeks postnatal age, as close to their expected date as possible. Therefore, the two groups were tested at similar conceptional ages. Table 1 presents the means, standard deviations, and ranges of values for gestational age at birth, as well as conceptional age and chronological age when tested with evoked

potentials. Nineteen full term infants were tested in the
neonatal period. In 1 infant, there was not sufficient time
to perform the somatosensory evoked potential. There were
nine low risk premature infants evaluated as close to term
as possible.

somatosensory evoked potentials:

Thirty five median nerves were tested in the newborn
period in the full term group; recordings from one median
nerve could not be obtained due to electrical artifact.
Both median nerves were tested in each of the 9 pre-term
infants.   All but 2 full term infants were asleep when
tested,   whereas 4 out of 9 premature infants were drowsy or
awake. One other premature infant was awake initially, but
fell asleep when the second limb was being stimulated.   In
the full term group, EP and CII were easily recognizable
whereas parietal potentials were present in 85%,   and
questionable or absent in 15%.   In the premature infants, 1
out of 18 EP potentials was not easily identifiable due to
electrical artifact,   however N13 (generated over the second
cervical vertebra) was easily recognizable in all cases.
For the parietal potential (N19), 1 out of 18 was
questionable,   being of very low amplitude and dispersed and
1 other potential was absent. The unilateral questionable or
absent potentials were found in comparable proportions in
the full term group (12).   It should be noted that
questionable or absent parietal potentials were not seen in
recordings of 2 month old full term infants (8 weeks

chronological age).

Wave shape in the 2 groups were similar in that EP and N13 were clearly identifiable whereas N19 was of low amplitude, broad based and dispersed. This is in contrast with the parietal potentials of the full term infants tested at 2-3 months of age, which are easily recognizable with increased amplitudes and smaller bases (Figure 1). It should be noted that the recordings selected in Figure 1 were representative examples of the morphologic characteristics of each group (i.e. A,B,or C), notwithstanding the child's level of consciousness during testing.

Latencies for EP, N13, N19 and interwave latencies for N13-N19, and N19-P22 appear in Table 2. T tests reveal no significant differences between the 2 groups. However, the mean latency of N13 was somewhat longer in the full term group (9.9 compared to 9.5; P=.0982), and this may be due to small differences in arm length between the two groups. In the full term infants, the mean arm length was 17.6 centimeters (+/- 0.85) whereas in the premature group it was 17.3 (+/- 0.87). Furthermore, the N19-P22 interwave latency was also of longer latency in the full term group (9.7 compared to 8.5; P=.1460). In a previous report from our laboratory (12), N19-P22 interwave latency was found to be prolonged by sleep in young infants In our subjects, 5/9 of the premature infants were drowsy or awake during recording sessions, whereas only 2/18 of the full term

infants were awake throughout the recording session.

N13-N19 interwave latencies represent central conduction time through the dorsal column-medial lemniscal system. A plot of N13-N19 values against conceptional age (gestational age + postnatal age) and against chronological age (postnatal age) can be compared in Figure 2 Clearly, the values for premature and full term infants of the same conceptional age (i.e. tested at term) are more similar in range and variability than in infants of the same chronological age (i.e. tested at approximately 6-10 weeks after birth).

auditory brainstem evoked potentials:

Thirty seven out of 38 ears were tested in the full term group and all 18 ears were evaluated in the pre-term group. Waves I, III and V were easily identifiable and the latencies for wave V and I-III and I-V interwave latencies are presented in Table 3. There are no significant differences between the 2 groups for these values.

DISCUSSION

The human fetus develops _in utero_ for approximately 38 weeks after conception With the advent of new life support systems, many premature infants are now exposed to the extrauterine environment up to 4 months earlier. Several studies argue that this precipitate exposure to the

extrauterine world may influence or facilitate the maturation of the nervous system. Discrepancies in neurologic functioning have been reported in clinical investigations comparing the neurobehavioral status of premature and full term infants tested at term (40 weeks conceptional age). Inferior performance in visual and auditory orienting as well as motor patterns have been documented in the premature group and authors suggest that the pre-term infants have poorer behavioral organization (15-17). Others have established that the neurobehavioral performance between the two groups is not significantly different (18-20). Palmer et al (21) assessed 80 preterm infants at 40 weeks conceptional age and compared them with full term infants. The premature infants were more alert and responded better to auditory and visual stimuli. They had less flexor tone and diminished arm traction and recoil. Amiel-Tison (22) suggested that there is a possible acceleration of neurologic maturation in premature infants with evidence of unfavorable intrauterine conditions. In a preselected group of premature infants (16 out of 1400 tested) neurologic age on examination was at least 4 weeks greater than the estimated gestational age.

In summary, there is considerable disagreement in the literature regarding the neurobehavioral performance of premature infants compared with full term infants tested at the same conceptional age. This may be partly due to the possible influences of perinatal and neonatal conditions on

neurologic functioning (i.e. low risk versus high risk prematures), the assessments used, the consistency of the state at the time of testing, and variation in neurologic development. Clearly, these studies have not shown that early exposure to the extrauterine environment impacts on myelination.

Myelination of axons begins in the second trimester of pregnancy and continues for many years after birth. This process begins in the periphery, and proceeds in a caudal-rostral direction. The hemispheres myelinate well after birth and the dispersed and immature peaks that are generated from parietal scalp recordings of the somatosensory evoked potential reflects this. The high variation in myelin deposition is manifested by the notable variability in latency values documented in neonatal somatosensory evoked potentials (23,24) Gestational age plus postnatal age is believed to be the most meaningful criterion for myelination (25). The nervous system evolves anatomically and physiologically in a predictable manner, therefore the neurologic exam may be used to estimate gestational age (7). Estimation of gestational age is important for the management of clinical problems, and for physiologic studies and developmental assessments (26).

Evoked potentials may be the most reliable quantitative indicator of accelerated or delayed myelination in the newborn (3,27,28). The components of the auditory brainstem evoked potential (i.e. latency, amplitude) show maturational

neurologic functioning (i.e. low risk versus high risk prematures), the assessments used, the consistency of the state at the time of testing, and variation in neurologic development. Clearly, these studies have not shown that early exposure to the extrauterine environment impacts on myelination.

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Evoked potentials may be the most reliable quantitative indicator of accelerated or delayed myelination in the newborn (3,27,28). The components of the auditory brainstem evoked potential (i.e. latency, amplitude) show maturational

changes as a function of gestational age. For example, the latency or conduction time decreases as a function of increasing gestational age. Furthermore, this maturational process proceeds at approximately the same rate, regardless of environment (intrauterine or extrauterine). Therefore, longitudinal and cross-sectional auditory brainstem evoked potential data may be pooled for a given conceptional age (4,5,9,10). Latencies between 28-40 weeks conceptional age vary too much to be used to predict conceptional age (4)

Somatosensory evoked potentials performed on healthy full term newborns demonstrate that potentials generated over Erb's point and the second cervical vertebra are easily elicited whereas the parietal scalp potentials are of low amplitude and dispersed and are occasionally absent (12,13) Maturational changes over the first six months are prominent, particularly for the parietal potential, and include decreased absolute and interwave latencies, increased amplitudes and diminished dispersion (12) Somatosensory evoked potentials in pre-term newborns are reliably recorded and demonstrate the same maturational changes that are classically seen with auditory brainstem evoked potential recordings (3,11). Maturation of the somatosensory evoked potential components appear to occur at the same rate regardless of environment in infants with no evidence of brain damage however this remains to be substantiated (11)

The aim of this study was to determine whether or not

somatosensory evoked potential normative data obtained from healthy full term infants could be utilized for premature neonates tested at term, as is the case for the auditory brainstem evoked potential Therefore premature infants with favoreable perinatal and neonatal conditions were tested with the somatosensory evoked potential at 40 weeks conceptional age and findings were compared with those obtained from full term infants.

The results demonstrate that there are no significant differences in absolute or interwave latencies of auditory and somatosensory evoked potentials at a given conceptional age, whether the infant was born at that age or matured to that age. Furthermore, waveform identifiability and wave shape of the potentials in pre-term infants tested at term resemble those of full term newborns, as opposed to full term 2 month old infants. Therefore normative data from healthy full term infants can be applied clinically to premature infants tested at similar conceptional ages.

Our study confirms the findings of Klimach & Cooke (11), in spite of quite variable somatosensory evoked potential stimulating and recording parameters. Other electrophysiologic tests such as electroencephalography and electromyography have provided further evidence that conceptional age rather than postnatal age dictates the maturational parameters of these tests (11). Accurate and age appropriate normative data is essential in maximizing the utility of evoked potential testing in the pediatric

population. Auditory brainstem evoked potentials are used widely as a neonatal hearing screening tool as well as to assess the functional integrity of the immature nervous system (14,29-31). Somatosensory evoked potentials may prove to be of tremendous value as a prognostic tool as the somatosensory pathway bipasses important areas of the brain that are vulnerable to hemorrhagic or ischemic brain injury particularly in premature infants. The predictive value of somatosensory evoked potentials in high risk newborns is presently being explored in a prospective study Preliminary findings indicate that the degree and persistence of neonatal somatosensory evoked potential abnormalities reflect the extent of neurologic impairment on follow -up (32).

FIGURES AND TABLES

Table 1

Gestational age as well as conceptional and chronological ages at testing in the full term and premature infants.

Table 2

Absolute and interwave latencies of the somatosensory evoked potential following median nerve stimulation in full term and premature infants tested at term.

Table 3

Absolute and interwave latencies of the auditory brainstem evoked potential in full term and premature infants tested at term.

Figure 1

A Comparison of a premature infant's somatosensory evoked potential recording with that of a full term infant (A) of a similar conceptional age and a full term infant (C) of the same chronological age.

Figure 2

A plot of N13-N19 interwave latency against conceptional age and against chronological age.

ACKNOWLEDGEMENTS

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TABLE 1

TESTING AGE (weeks)

	mean	s.d.	range
FULL TERM			
gestational age*	39.2	1.5	37-42
conceptional age	39.5	1 7	37-43
chronological age	0(<1)		
PREMATURE			
gestational age	34.0	1.7	32-36
conceptional age	39.8	1.1	39-42
chronological age	5.7	1.7	3-8

*at birth

TABLE 2

SOMATOSENSORY EVOKED POTENTIALS
ABSOLUTE AND INTERWAVE LATENCIES

	EP	N13	N19	N13N19	N19P22
FULL TERM	N=35	N=35	N=31	N=31	N=31
mean	6.3	9.9	24.6	14.8	9.7
s.d.	(0.71)	(0.73)	(3.13)	(2.83)	(2.95)
PREMATURE	N=17	N=18	N=16	N=16	N=16
mean	6.2	9.5	24.8	15.2	8.5
s.d	(0.61)	(0.85)	(2.23)	(2.69)	(1.81)

TABLE 3

AUDITORY BRAINSTEM EVOKED POTENTIALS
ABSOLUTE AND INTERWAVE LATENCIES

	I-III	I-V	V
FULL TERM	N=37	N=37	N=37
mean	2.7	4.8	7.0
s.d.	(0.25)	(0.30)	(0.42)
PREMATURE	N=18	N=18	N=18
mean	2.6	4.7	7.0
s.d.	(0.32)	(0.35)	(0 40)

FIGURE 1

A. Full Term (Newborn)
Conceptional Age: 38 weeks
Chronological Age: 5 days

B. Premature Infant
Conceptional Age. 39 weeks
Chronological Age: 7 weeks

C. Full Term (2 months)
Conceptional Age: 48 weeks
Chronological Age: 7 weeks

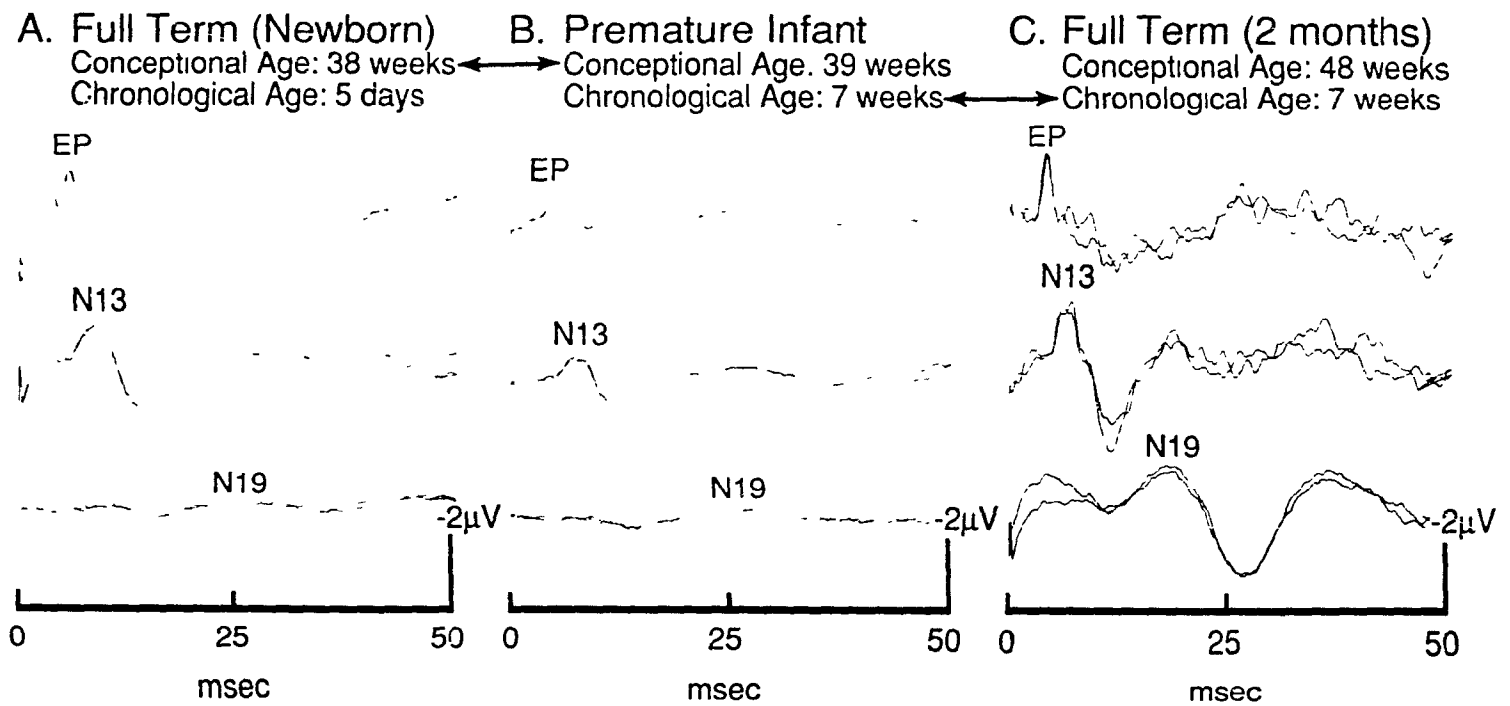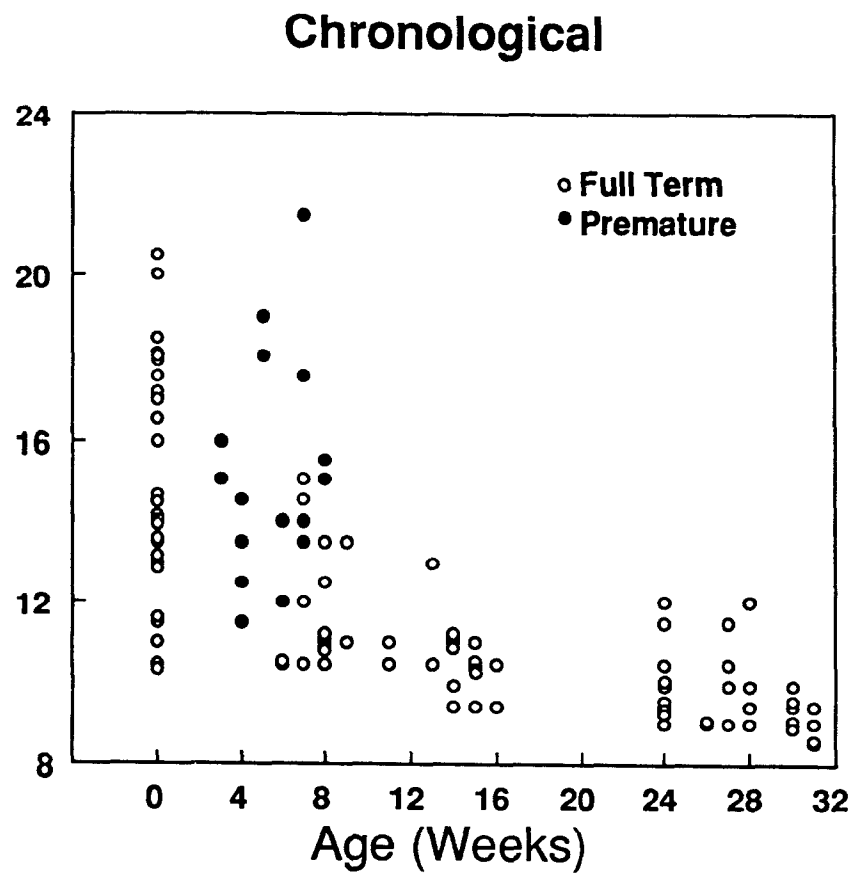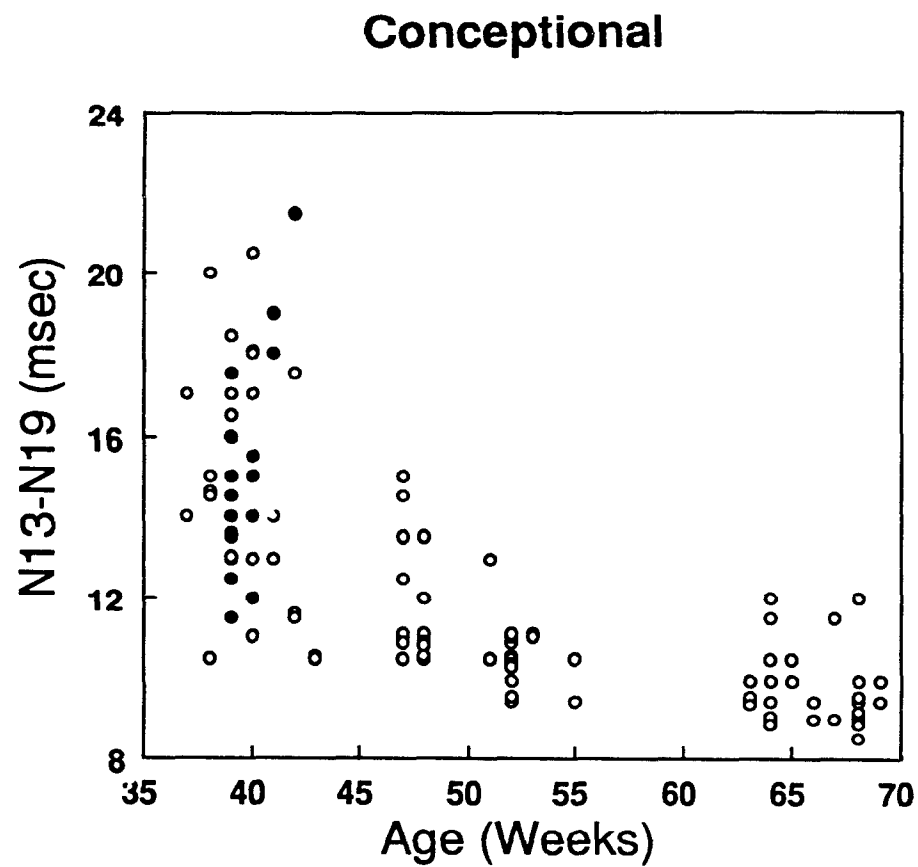FIGURE 2

Somatosensory Evoked Response Abnormalities in High-risk Newborns

Annette Majnemer, MSc*+, Bernard Rosenblatt, MDCM*++, Patricia Riley, MDCM§‡,
Emmanuele Laureau, MD*, and Augustin M. O'Gorman, MB,BCN†¶

In a previous study from our laboratory, the prognostic significance of the auditory brainstem evoked response was assessed in high-risk neonates. An abnormal auditory brainstem evoked response predicted neurologic deficits at age 1 year, however, a normal result did not predict a normal outcome. In order to evaluate the prognostic utility of examining other sensory pathways, somatosensory evoked responses were elicited following median nerve stimulation. Testing was performed at 37-44 weeks conceptional age (defined as gestational age plus chronologic age) and at 2 and 6 months conceptional ages. Those patients studied included 34 high-risk neonates and 18 healthy, term infants as controls. Ten of the 34 patients had abnormal somatosensory evoked responses. Abnormalities included increased absolute (N19, P22) and interwave (N13-N19, N19-P22) latencies and flat potentials, alone or in combination. Three children with flat potentials demonstrated a persistence of this abnormality on subsequent examination and they later presented clinically with spastic quadriparesis. Four infants with increased latencies manifested normal responses on subsequent examination. Recently, these 4 patients exhibited tone abnormalities and mild developmental deficits; developmental outcome, however, will be assessed in a blind study at 1 year of age as part of this ongoing prospective study. Preliminary results suggest that somatosensory evoked responses may be valuable as an electrophysiologic predictor of outcome.

Introduction

Short-latency somatosensory evoked responses (SSERs) are widely used to assess the integrity of the sensory pathway as it projects from the periphery to the contralateral parietal cortex [1] Stimulating and recording parameters are highly variable (i.e., nerve stimulated type of stimulus, rate, montage, filter setting), therefore, it is difficult to compare normative data among laboratories Different waveforms with a variety of nomenclatures have been described [2-4] There are few reported clinical studies of SSERs in newborns and infants. The neonatal, parietal potential (N19, N20, or N1) typically has very low-amplitude, is dispersed, and occasionally is not detectable in healthy newborns The percentage of potentials detected in healthy newborns has been variable, ranging from 50% [5], to 67% [6], and up to 85% [7] A parietal potential is detectable on at least one side in all healthy newborns Furthermore, subsequent testing at 2 months of age demonstrates that parietal potentials are always clearly identifiable Potentials at Erb's point (EP) and over the cervical vertebrae are morphologically more clearly defined and can be reliably obtained in all newborns [7] In infancy, maturational changes in SSER include decreasing absolute and interwave latencies and increasing amplitudes as a function of age [2-6 8-13]

There has been some recent interest in using evoked responses as objective diagnostic and prognostic tools in the neonatal intensive care unit (NICU) [14-17] Clinical applications of SSERs in newborns at risk for neurodevelopmental sequelae have not been adequately explored therefore, we began a prospective study with the following objectives

(1) To delineate a technique for performing SSERs in infants that produces reliable recordings,

(2) To establish normative data for SSEPs in newborns and infants,

(3) To compare findings in normal and high-risk neonates, and,

(4) To determine the predictive value of SSERs and auditory brainstem evoked responses (ABRs) Results of the first two objectives were reported previously [7] This study describes the SSER findings in 34 high-risk newborn infants and also explores the relationship between electrophysiologic abnormalities and developmental status in infancy
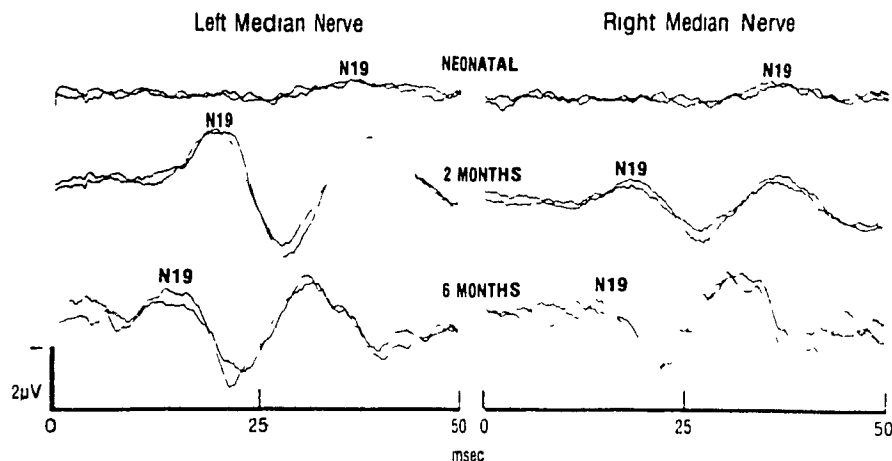
Left Median Nerve   Right Median Nerve

Figure 1   Increased latencies of N19 and P22 normalized on subsequent testing at 2 and 6 months cor rected age

Methods

Healthy newborns comprised the control group Controls were born at term (37-42 weeks conceptional age) with Apgar scores of 8-10 at 5 min, birth weights appropriate for gestational age, and no perinatal complications Patients were selected from three groups at risk for neurodevelopmental sequelae as a result of anoxic-ischemic injury The groups included asphyxiated infants small-for-gestational-age infants or very low-birth weight newborns Infants were considered to be asphyxiated if the Apgar score at 5 min was ≤ 7 and/or positive pressure ventilation was required for at least 2 min Patients with good Apgar scores who had clinical histories suggestive of asphyxia (ie 2 of the following intrapartum history suggestive of asphyxia clinical syndrome in the first week of life computed tomography [CT] compatible with hypoxic changes) also were included in this group The very low-birth weight group consisted of preterm infants who had birth weights < 1 501 gm yet appropriate for gestational age Small-for-gestational-age infants included those with birth weights below the 3rd percentile for gestational age

Controls and patients were tested in the newborn period (37-44 weeks conceptional age) with ABR and SSER Evoked responses were repeated at 2-3 months and 6-7 months corrected age SSER findings in the 34 high-risk newborns are presented in this report In order to determine the predictive value of evoked responses controls and patients

were examined for neurodevelopmental status at 1 year corrected age by a neurologist and psychologist unaware of each patient's status

SSER Testing Controls and patients were tested in a quiet room, none of them was tested in the NICU Newborns generally were either drowsy or asleep during testing Infants were retested while they were awake

An electrical square wave pulse was delivered to each median nerve using an infant stimulating electrode at a rate of 4 Hz and duration of 200 usec with an intensity sufficient to produce a minimal thumb twitch

Gold cup electrodes were placed at EP over CII and 2 cm behind C3 and C4 (as defined by the 10-20 system) electrodes were referenced to Fz Filters were set at 30-3 000 Hz and input was amplified 100 000x Responses numbering 512 were averaged at least twice to ensure reproducibility of the waveforms Two trials were superimposed on the x-y plotter Absolute and interwave latencies of EP, N13, N19 and P22 were measured by 2 individuals independently

Results

Eighteen healthy control newborns were tested between 37- 42 weeks conceptional age, 13 of whom participated in all subsequent testing Thirty-four high-risk newborns were
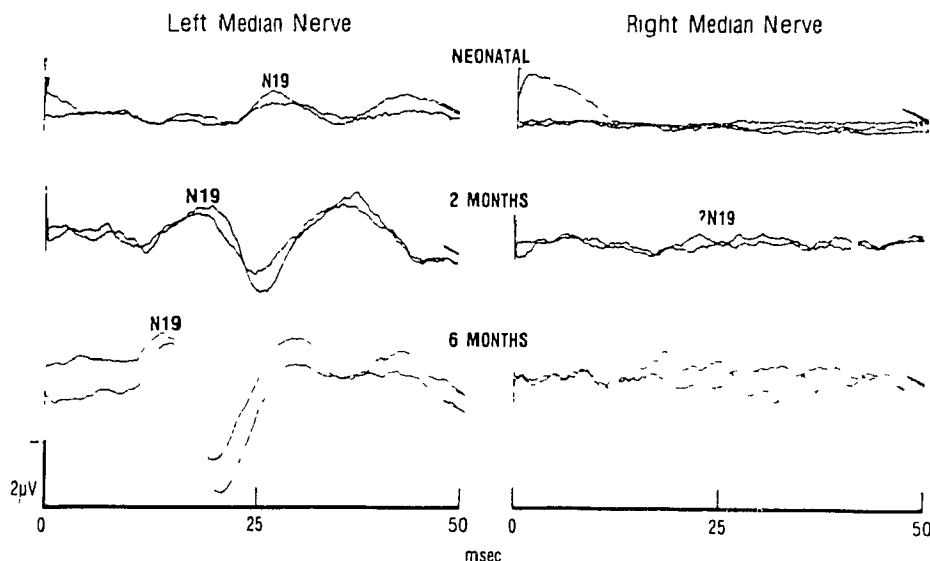
Left Median Nerve   Right Median Nerve

Figure 2   SSER performed in the neonatal period demonstrated a normal potential following left median nerve stimulation and a flat response after right median nerve stimulation This abnormality persisted on serial testing

2 MONTHS

Left Median Nerve   Right Median Nerve

EP

EP

CII   CII

2μV
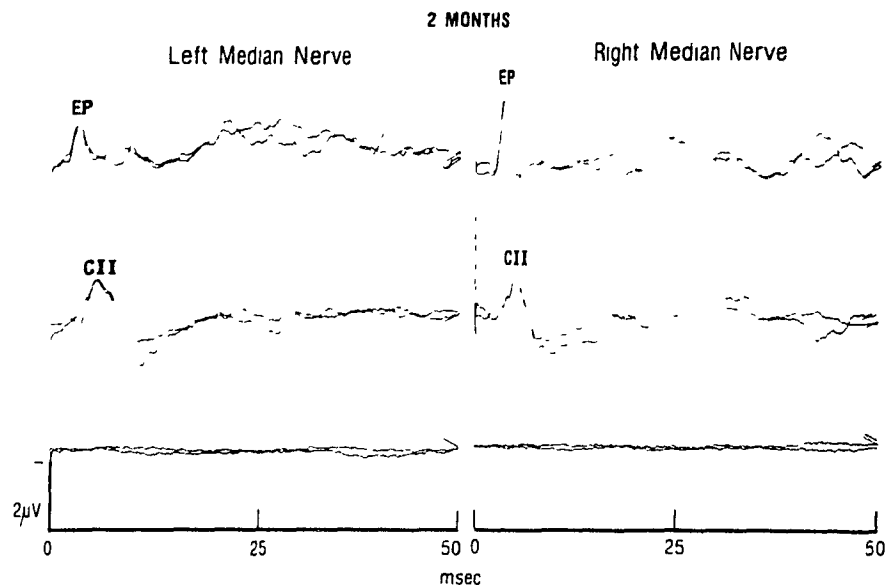
0   25   50 0   25   50

msec

Figure 3   Flat, bilateral potentials (N19) were observed in the newborn period and again on subsequent testing. Potentials at Erb's point and over CII were normal indicating normal transmission at root entry and in the distal lemniscal pathway.

included in this longitudinal study, 32 of whom had SSERs in the newborn period when they were stable and able to leave the NICU Testing was performed as close to 40 weeks conceptional age as possible (range 37- 45 weeks) Evoked responses were repeated at 2-3 and 6-7 months corrected age as was the control group.

Mean and standard deviations for both absolute and interwave latencies were established in the control group for each age level (i e , newborn, 2 months, 3 months, and 6-7 months) In the newborn period, EP and C2 were present in all patients Parietal potentials were clearly identifiable in 85% of patients, questionable in 6% (i e , very low-amplitude, < 22 μV deflection), and absent in 9% Each control had a clearly reproducible N19 on at least one side Minimal changes in latency and waveform morphology at EP and CII were observed on serial testing; however, there were marked alterations in the parietal potential, including decreased latencies and waveform duration and increasing amplitude [7] By 2 months corrected age, N19 always was clearly identifiable bilaterally

SSER recordings of the high-risk newborns were compared with those of the controls and 10 of 34 had abnormal findings. Five of these 10 patients had birth weights below 1,500 gm and 6 of 10 were asphyxiated premature infants. Fifty percent of the premature infants in our study (12 patients) of high-risk newborns had SSER abnormalities, whereas only 18% of the term high-risk newborns (22 patients) had abnormal recordings. Of the 10 high-risk newborns with abnormal SSERs, 7 had normal ABR interpeak latencies and V/I amplitude ratios Two infants with abnormal SSERs (i e , flat, bilateral, parietal potentials) and ABRs (i.e., increased interpeak latencies) were severely asphyxiated and suffered severe neurologic sequelae

The types of abnormality in the N19 waveform included

(1) Increased absolute (N19, P22) and interpeak latencies (N13-N19, occasionally N19-P22) > 2 5 standard deviations of the mean of the age-matched control group;

(2) Flat, bilateral, parietal potentials, bilaterally questionable N19, or unilaterally flat potentials that persisted on subsequent testing at 2 months of age,

Left Median Nerve   Right Median Nerve

2 MONTHS

N19

N19   6 MONTHS   ?N19
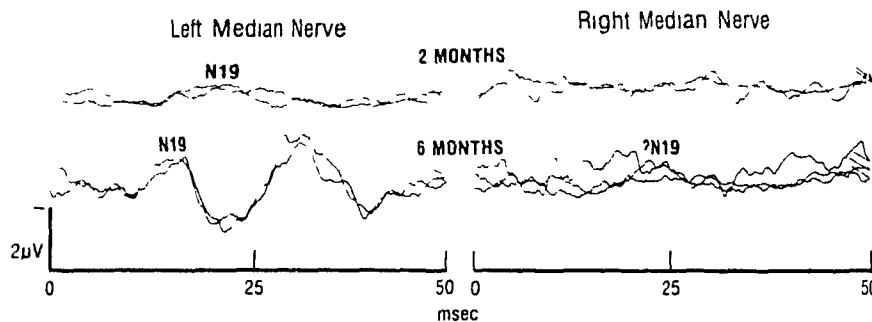
2μV

0   25   50 0   25   50

msec

Figure 4   An increased latency of N19 on the left side became normal by 6 months of age, whereas a flat response on the right side remained abnormal in latency

| Left Median Nerve | | Right Median Nerve |

NEONATAL

N19 Awake / Asleep   N19 Drowsy

2 MONTHS
N19

6 MONTHS
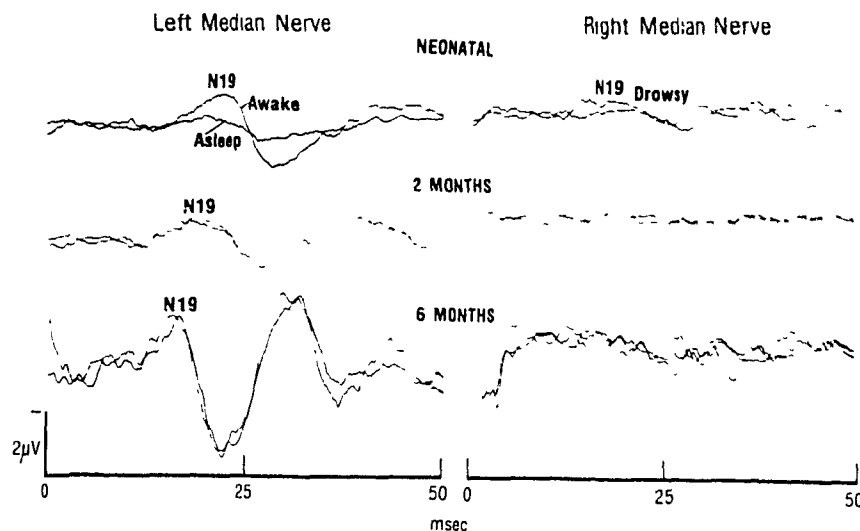N19

2μV

0   25   50   0   25   50
msec

Figure 5   The initial SSER revealed normal N19 potentials bilaterally however, there was flattening of the potential on the right side at 2 and 6 months of age

(3) A combination of 1 and 2 one side flat and one side with increased latencies, and,

(4) SSER that was normal initially but was abnormal on subsequent testing

There were 4 patients with increased absolute and inter-wave latencies (N19, P22, N13-N19) in the newborn period 2 unilaterally and 2 bilaterally All 4 patients were asphyxiated premature babies, 3 of whom were very low-birth weight (< 1,501 gm) On subsequent testing at 2-3 months of age, all SSERs normalized (Fig 1) Currently, these children have muscle tone abnormalities and mild developmental delays, however, clinical status will be assessed at 1 year corrected age

There were 3 patients with flat parietal potentials (N19) in the newborn period 1 unilaterally (Fig 2) and 2 bilaterally (Fig 3) There was an additional patient with questionable recordings bilaterally All 4 patients demonstrated a persistence of SSER abnormality on subsequent testing The 3 patients with flat recordings have spastic quadriparesis The child with unilateral flat recordings (Fig 2) has greater involvement on the side corresponding to the flat response

One patient could not be tested in the newborn period because he was medically unstable and could not leave the NICU At 2 months corrected age, however, SSER demonstrated a combination of abnormalities with the right side (i e , right median nerve) being flat and the left side having increased latencies At 6 months of age, the right side had a recognizable potential with increased latencies, whereas the left side was within normal limits (Fig 4) Neurologic examination at 1 year of age demonstrated a spastic diplegia greater on the right side

One patient had a normal SSER in the newborn period which became abnormal on subsequent testing CT performed in the first week of life demonstrated a left fronto-parietal infarct SSER performed at 2 months of age demonstrated a flattening of the N19 waveform on the side corresponding to the evolving brain injury This abnor-

mality persisted at 6 months of age when the child also had a hemiparesis (Fig 5)

Radiologic Findings Thirty-two of 34 patients had ultrasounds and/or CT scans performed in the newborn period (< 44 weeks conceptional age) All radiologic films were reviewed by a radiologist retrospectively so that the relationship between early SSER testing and neuro-radiologic investigations could be explored The radiologist was unaware of the SSER results when scoring the radiologic investigations Findings were scored as demonstrating

(1) Normal findings,
(2) Anoxic changes (i e , minimal, moderate, severe),
(3) Hemorrhage (grade III-IV), or,
(4) Ventriculomegaly without hemorrhage

Thirteen of 32 patients had normal radiologic findings, 10 of whom also had normal SSER recordings There were 4 patients with Grade III-IV hemorrhage, 2 had normal SSERs, and 2 had abnormalities corresponding to the side of hemorrhage There were 13 infants demonstrating radiologic evidence of anoxic changes Five had minimal, nonspecific changes, 5 had moderate anoxic changes, and 3 had severe anoxic changes Four of 13 children with anoxic changes had abnormal SSERs

Discussion

There are few reported clinical studies of SSERs in high-risk newborns Lutschg et al. [18] performed ABRs and SSERs on 10 asphyxiated babies at 3 months of age All 10 had abnormal tone and neuroradiologic evidence of severe leukomalacia and cortical atrophy ABRs were normal or slightly prolonged, however, there were no cortical SSERs detectable in the newborn period or at 3 months of age.

Hrbek et al [19] reported that SSERs were of low-amplitude and were dispersed or absent in 65% of 57 asphyxiated newborns Those patients with persistent abnormalities had clinical evidence of brain injury

Laget et al [20] tested 43 children ranging in age from 14 days to 13 years All had localized motor deficits, such as hemiplegia or monoplegia The authors reported that SSER was more accurate than electroencephalography (EEG) in localizing and lateralizing the lesion and suggested that SSER may be useful in early diagnosis of brain damage

Recently, Gorke [21] investigated the prognostic value of SSER in 73 infants with a variety of peri- and post-natal problems and impaired neurodevelopment Initial testing was performed between 1-10 months of age Forty-seven infants with minor perinatal risk factors and normal developmental outcomes were chosen retrospectively to be the control group There were 19 infants with significantly increased NI (i e N19) peak latencies or absence of potentials all of whom demonstrated handicap after the first year of life (range in age 11-36 months) Impairments included psychomotor retardation, cerebral palsy, and degenerative and metabolic diseases of the central nervous system Gorke concluded that SSER is valuable as an early indicator of severe motor impairment The author reported that there were false negatives (19/38) because this test examines the afferent sensory pathway exclusively, other areas may be impaired

In the study by Gorke, patients were assessed because of early evidence of neurologic deficits The high-risk group included many infants with degenerative diseases in whom prognoses are easily predicted, therefore, high-risk newborns with no clear evidence of brain injury in early infancy were not part of the experimental group The control group included infants with minor risk factors and slightly abnormal SSERs in infancy, thus, subtle, yet significant, electrophysiologic abnormalities could not be evaluated in this study

In our prospective study, healthy and high-risk newborns could be differentiated by SSER testing When comparing the findings with the normative data established in our laboratory, we found that SSER abnormalities occurred in approximately one-third of newborns at risk for neurodevelopmental sequelae Abnormalities included increased absolute (N19, P22) and interwave (N13-N19 primarily) latencies, and flat potentials alone or in combination These abnormalities were detected in the newborn period (i e , 37-44 weeks conceptional age) and were characteristically observed in asphyxiated premature infants The potential at EP was identifiable in all patients, N13 was present and of normal latency in all but one patient who had flat N13 and parietal potentials initially and who demonstrated severe neurologic impairment in infancy

Controls and patients were retested at 2 and 6 months postconceptional age for evaluation of waveform evolution Patients who previously had increased latencies had normal recordings on subsequent testing at 2-3 months of age These patients also demonstrated mild neurologic manifestations of brain injury in infancy Three children with flat parietal potentials, all of whom have spastic quadriparesis, demonstrated persistence of this abnormality on subsequent recordings. One child had increased latencies on one side and a flat response on the other; neurologic exa. ination at 1 year of age revealed that the child had spastic o.plegia with more involvement on the side corresponding to the flat potential There was one newborn who had a large hemispheric infarct with a normal SSER initially that flattened on re-evaluation at 2 and 6 months of age. This result may reflect the gradual pathologic changes that occurred in cerebral tissue following the infarct.

CT scans and ultrasounds were analyzed and scored blindly by a neuroradiologist and were found not to correlate strongly with initial SSER findings Radiologic findings provide evidence for structural lesions, whereas SSER abnormalities indicate dysfunction in neuronal transmission as a result of brain injury, therefore, one would not expect a perfect correlation between these two diagnostic tools One patient demonstrated minimal anoxic changes on CT, demonstrated a persistent, flat, bilateral SSER, and at 1 year of age presented with spastic quadriparesis Conversely, there was one child who had profound anoxic alterations on CT, had an epileptiform EEG, and demonstrated increased tone in the first few months of life. SSER was normal and at 1 year of age the child had a normal neurologic examination and normal developmental scores Therefore, it appears that SSER may provide useful information to the clinician regarding the functional integrity of neuronal pathways

Previous studies reported associations between severe leukomalacia as well as developmental handicap and abnormal SSERs In our study, one-third of the high-risk neonates had SSER abnormalities in the newborn period. The extent and evolution of the abnormalities appeared to reflect the degree of anoxic-ischemic injury to the central nervous system All patients (i e , those with normal or abnormal recordings) and controls are being evaluated currently at 1 year corrected age in a blind study by a neurologist and psychologist for neurologic status and developmental progress The predictive value of SSERs remains to be determined in this ongoing prospective study

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THE PROGNOSTIC SIGNIFICANCE OF MULTI-MODALITY
EVOKED RESPONSE TESTING IN HIGH RISK NEWBORNS

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ABSTRACT

Exposure to hypoxic-ischemic events in fetal or neonatal life may lead to permanent brain damage and subsequent neurodevelopmental deficits. Clinical and diagnostic tools have been somewhat helpful in identifying an at-risk group, particularly in those sustaining significant neurologic sequelae. In this prospectve study, the prognostic significance of multi-modality evoked responses in high risk newborns was examined. A group of 44 high risk newborns as well as 14 healthy newborns were tested in the newborn period with auditory brainstem (ABR) and somatosensory (SER) evoked responses, and these tests were repeated at 2 and 6 months corrected age. A neonatal neurological exam, the Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS) was performed as well. At 1 year corrected age, healthy and high-risk groups were assessed in a blind fashion by a pediatric neurologist and a psychologist to determine neurodevelopmental outcome. Results show that SER abnormalities in particular predict an abnormal neurologic status at 1 year of age. Abnormalities that persisted or worsened correlated with severe neurologic impairment whereas an abnormal SER that improved or normalized in infancy was associated with mild to moderate neurologic sequelae. Increased brainstem conduction in the ABR was also associated with neurologic sequelae. A normal ABR and SER predicted normal developmental scores in all areas as well as a normal neurologic outcome at 1 year with

negative predictive powers ranging from 85-100%. Evoked response testing appears to be an important adjunct to the neurologic investigation of high-risk newborns.

INTRODUCTION

Newborns who have suffered anoxic-ischemic injury to the brain as a result of prenatal, perinatal and/or postnatal complications are considered to be at "high risk" for neurodevelopmental sequelae. Handicaps may include motor disturbances, seizures, blindness or deafness, behavior disorders, and developmental retardation.[1,2] Major handicap is usually evident by the end of the first year of life, however more subtle developmental deficits such as poor eye-hand coordination, learning and behavioral problems, and disorders of language may go undetected for several years.[3] It is important to identify infants that are likely to suffer neurologic sequelae so that these children are followed closely and managed effectively.[4-5]

A variety of behavioral, neuroradiologic and electrophysiologic measures have been employed in this population in an effort to predict neurologic outcome. Recent studies have been insightful regarding the level of central nervous system dysfunction, particularly in those infants that are either severely affected or normal on follow-up.[6-10] Experimental models of perinatal anoxic-ischemic insult as well as human neuropathologic studies have demonstrated that a host of brainstem, thalamic, cerebellar and cerebral structures such as the gracile and cuneate nuclei, the cochlear nuclei and inferior colliculi, the ventroposterior aspect of the thalamus and the pre and post

central cortices are selectively vulnerable to anoxic/ischemic insult in the maturing brain.[7,11-16] The somatosensory and auditory brainstem evoked response (SER and ABR) assess the integrity of the ascending neuraxis and abnormalities in these tests may reflect direct injury or maldevelopment to structures along the sensory pathways. These diagnostic tools may determine the severity of the insult and may be useful clinically in monitioring recovery.[4,17-21]

In a previous prospective study, the neonatal ABR was found to have a high specificity and strong positive predictive power for neurologic abnormalities at one year of age in high risk newborns, however a normal ABR did not ensure a normal outcome.[22] The SER also evaluates structures rostral to the brainstem, and therefore a wider distribution of the central nervous system could be evaluated using both the ABR and SER. The aim of this study was to determine the predictive value of multi-modality evoked responses in a group of newborns that are at risk for neurodevelopmental deficits. High risk newborns as well as healthy neonates were tested in the newborn period and again in infancy, and evoked response findings were correlated with neurologic and developmental outcome at one year corrected age.

METHODS

Subjects

All admissions to the Montreal Children's Hospital

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neonatal intensive care unit were reviewed weekly and patients considered to be at risk for neurologic sequelae as a result of hypoxic-ischemic injury were registered into the study. Criteria for inclusion into the study included: 1)very low birthweight (<1501 grams 2)small for gestational age (below the 3rd percentile) and 3)asphyxia (Apgar of 7 or less at 5 minutes, > 2 minutes of positive pressure ventilation, or clinical syndrome of asphyxia.)[22] Newborns with congenital neurologic malformations or dysmorphic features were excluded. Patients transferred back to the referring centers who would not be followed at this tertiary center were eliminated from this study.

Controls

A control group was obtained from a well-baby nursery. All newborns were 37-42 weeks gestational age, with Apgar scores from 8-10 at 5 minutes, and birthweights appropriate for gestational age. Prenatal and perinatal histories were unremarkable.

Experimental design (figure 1)

Informed consent was obtained from the parents of all subjects and controls prior to any testing. The protocol for this study was approved by the hospital's scientific and ethics committees.

Evoked response testing was carried out in the evoked response laboratory for the subjects and in a quiet room adjacent to the well-baby nursery for the controls.

Sedation was not required. ABRs and SERs were performed when patients were medically stable, as close as possible to 40 weeks conceptional age (defined as gestational age plus chronological age). Controls were tested on day 2 or 3 of life. A standardized neurologic evaluation, the Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS), was also done on controls and subjects as close as possible to the due date. Patients that could not be tested include those who were medically unstable at this time or those who were discharged prior to testing. Some patients were either very sleepy or irritable, therefore the ENNAS could not reliably be done.

Evoked responses were repeated in infancy. In a previous study on ABRs in high risk newborns[22], any abnormalities in the response either normalized by 2 months of age or remained abnormal, with no further changes at 6 months. Therefore the ABR and SER were repeated at 2 months of age, and the SER alone was done at 6 months. At 1 year corrected age, subjects and controls were tested in a blind fashion by a psychologist using the Griffiths Developmental Scale and by a pediatric neurologist (BR). Evoked response findings as well as the ENNAS deviant score (defined as the number of abnormal items obtained out of 22) were correlated with developmental and neurologic scores at 1 year of age.

Evoked response testing

SERs were generally performed while the patient was awake and feeding, whereas the ABR was done while the infants were sleeping. In all cases, gold cup electrodes were applied with electrode paste and impedances were maintained below 5 Kohms. Trials were repeated at least twice to ensure waveform reproducibility. Recordings were scored by A.M. immediately after testing.

SER:

Short latency SER studies were performed and evaluated as described in a previous study.[23] An electrical square wave pulse was applied to each median nerve at a rate of 4/sec and a duration of 0.2 msec. The intensity of stimulus was adjusted to produce a minimal thumb twitch. Recording parameters are listed on Table 1. Results were compared to normative data established in our laboratory. Absolute (N19) or interwave (N13-N19) latencies falling above 2.5 standard deviations of the mean of the age-matched control group or an N19 peak that was not identifiable were considered to be abnormal.

ABR:

Monaural rarefaction click stimuli were applied to each ear individually at a rate of 11.1/sec, and at an intensity of 70 decibels hearing level (dBHL). Intensities were increased if waveforms were difficult to identify. With decreasing intensities at a rate of 31/sec, threshold was established. Recording parameters appear on Table 1.

Abnormalities in I-III/I-V interwave latency, V/I amplitude ratio, as well as waveform dispersal and morphology were identified based on previously established criteria.[22]

ENNAS:

The Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS) is a 22 item standardized neurologic evaluation that is performed as close to 40 weeks conceptional age as possible on those subjects that can be handled easily. This assessment requires that the patient be tested in a quiet, alert state. All controls were tested prior to discharge from the well-baby nursery, whereas high risk newborns were tested when feasible prior to discharge. Items were rated individually as pass or fail based on established criteria, and a deviant score > 3 (4 or more items failed) was considered to be abnormal.

Outcome measures:

The Griffiths Developmental Scale contains 5 subscores for locomotor, personal/social, hearing and speech, eye and hand coordination, and reasoning skills. A general quotient is derived as well. Scores falling more than 2 standard deviations below the mean of the age-matched control group were felt to be abnormal.

A pediatric neurologist examined all subjects and controls and scored the exam as normal or abnormal. In particular, the examiner noted developmental milestones, general behavior, head circumference, reflexes, tone and

specific motor disability.

RESULTS

Forty-six out of 51 high risk newborns fitting our criteria agreed to participate in this prospective study however 2 dropped out in infancy, therefore yielding 44 subjects (86.5% consented). The risk factors of our study group appear on Table 2. Nineteen controls were obtained for neonatal testing, and 13 participated in all follow-up assessments to 1 year of age. Thirty-eight out of 44 high risk infants were tested on 3 occasions with evoked responses (newborn, 2 months, 6 months), 5/44 were tested twice, and 1 patient was tested in the neonatal period only. Evoked responses were performed on all controls on 3 or 4 occasions.[23] At 1 year corrected age, subjects and controls were evaluated by a pediatric neurologist and psychologist. One subject died at 4 months of age, 2 subjects were assessed by the psychologist only and 2 more infants only had a neurologic examination.

Age tested

The mean gestational age for subjects was 36.4 weeks ± 4.8 (25-42 week range), and for controls it was 39.2 weeks ± 1.5 (37-42 week range). Neonatal evoked responses were performed at 40.9 weeks conceptional age ± 1.9 (37-45 weeks) in subjects and at 39.5 weeks conceptional age ± 1.7 (37-43

weeks) in controls. Although this difference is significant, there were no maturational changes associated with the SER responses from 37 to 43 weeks conceptional age. Normative data for the ABR included findings from the control group of this study as well as a previous study using the same evoked response testing parameters.[22] The ABR measurements were then derived for 3 subgroups with conceptional ages of 37-39 weeks, 40-41 weeks and 42-45 weeks. Therefore ABR results in high risk infants were compared to the appropriate age-matched normative data. At 1 year of age, neurodevelopmental assessments were carried out at 12.3 months ±0.9 (10.1-16.0 months) in the high risk group and at 12.1 months ±0.5 (11.4-13.0 months) in the control gorup with no significant difference between groups.

Test performance

Abnormalities in the SER included 1)increased N19 peak latency and/or N13-N19 interwave latency > 2.5 standard deviations of the mean of the control group 2)unilaterally absent N19 peak that remained abnormal on follow-up 3)bilaterally absent N19 peaks 4)a normal SER recording that became abnormal at 2 and 6 months. Two patients had normal SERs at 2 and 6 months but missed the neonatal SER and therefore could not be categorized as normal or abnormal. Fifteen out of 42 subjects (35.7%) had abnormal SERs. In 5/15, the response abnormalities persisted to 6 months of age. In these patients, N19 was either persistently absent,

or significantly prolonged in latency in the newborn period and no longer identifiable in infancy. Ten out of 15 had predominantly prolonged central conduction time (i.e N13-N19) unilaterally or bilaterally, and on serial testing, there was improvement and sometimes normalization of the recordings.

Only 4 out of 43 subjects (9.3%) tested had abnormal I-III and/or I-V interwave latencies on the ABR. Fourteen out of 43 had abnormal morphology scores, 4 had abnormal V/I amplitude ratios and 4 had abnormal dispersal ratios. In this cohort, the incidence of ABR abnormalities was considerably reduced when compared to the results in the first prospective study on the ABR as a predictor.[22]

When comparing test performance in subjects and controls, t tests revealed significant differences in central transmission time for the SER (p<.05) and ABR (37-39 week subgroup = p<.05). The Wilcoxin Rank Sum 2 sample test (with continuity correction of 0.5) was used to compare all ordinal scale scores (i.e. neurologic exam, ENNAS deviant score) and ratios (i.e. dispersal and V/I amplitude ratios) obtained between high risk and healthy newborns. The ABR morphology score (p<.005), and the dispersal ratio for one subgroup (40-41 weeks= p<.01) were found to be significantly different. As might be expected, neurologic assessment of healthy and high risk infants in the newborn period and at 1 year of age were significantly discrepant

(p<.001 and p<.05 respectively). For the ENNAS neonatal neurologic exam, 13/29 subjects (44.8%) tested had abnormal deviant scores, whereas all controls (N=17) had normal deviant scores between 0 and 3. For the neurologic exam at 1 year, all controls had normal examinations, whereas 36% of high risk newborns had abnormal findings such as spastic quadriplegia (N=5), spastic diplegia (N=6), hemiplegia (N=2) and microcephaly (N=2). Although there were no significant differences in the subscores of the Griffiths Developmental Scale, the mean scores were generally lower and the variation or standard deviations were considerably greater in the high risk infants, particularly for motor and reasoning skills.

Prediction of outcome

Chi square analysis (with continuity correction of 0.5) was used to analyze relationships between the neonatal tests (i.e. ENNAS, ABR, SER) and neurodevelopmental outcome at 1 year of age. Sensitivity, specificity and predictive power of the neonatal assessments were derived as well.

i. ENNAS

The neonatal neurologic assessment (ENNAS) was a poor predictor of neurologic status at 1 year of age. Furthermore, an abnormal ENNAS deviant score did not correlate with low scores on the Griffiths Developmental Scale as there were many false positives. However, a normal score on the neonatal exam had a good negative predictive

power for each of the developmental subscales as well as the cumulative developmental score (general quotient), ranging from 75-94%. In other words, of 16 high risk newborns with normal scores on the ENNAS, most (ranging from 12-15) infants obtained normal scores in each of the areas of development tested in the Griffiths Scale. There was no significant relationship between the ENNAS and findings on the ABR and SER.

ii. SER

There was a significant relationship (p<.001)between the SER and the neurologic exam at 1 year of age (Table 3). Forty patients had SER testing and a neurologic exam at 1 year of age. Eleven out of 14 high risk infants with abnormal SERs had an abnormal neurologic exam at 1 year yielding a positive predictive power of 79%. The 3 "false positives" with abnormal SERs and normal neurologic exams all had a normal SER by 2 months of age. All 3 with normal neurologic outcome were noted to have short attention spans by the examiners at 1 year, and 2/3 had abnormal scores in adaptive and reasoning skills. Twenty three out of 26 patients with normal SERs had normal neurologic exams, yielding a negative predictive power of 88%. All 3 "false negatives" had mild spastic diplegia. Sensitivity and specificity were 79% and 88% respectively.

SERs were further ranked as persistently abnormal (persistently flat, or abnormal recordings that became flat on follow-up), abnormal but improving on follow-up, or

normal. A 3X2 chi square table (Table 4) reveals a significant relationship (p<.001) between the degree of SER abnormality and neurologic outcome at 1 year. All four with persistently abnormal SERs had significant neurologic sequelae (3 with spastic quadriplegia and limited developmental milestones, and 1 hemiplegic infant). There was 1 other patient with a flat SER in the neonatal period and at 2 months of age. This child was severely delayed with poor suck and swallow and spastic quadriparesis, and she subsequently died at 4 months of age. Seven out of 10 infants with milder abnormalities on the SER had neurologic deficits at 1 year. Neurologic abnormalities included microcephaly and mild hypertonia (spastic quadriplegia, spastic diplegia or hemiplegia). The evolution of all SER abnormalities and the subsequent neurodevelopmental findings at 1 year are outlined for each patient in Table 5.

The relationship between the SER and developmental scores at 1 year was less consistent. However, there was a significant correlation between a persistently abnormal SER and the locomotor score (P<.005), as 3/4 had abnormal gross motor scores whereas the 4th had a borderline score Furthermore, a normal SER or one that was abnormal initially but improved on follow-up was compatible with normal locomotor scores in 32/36 patients.

The analysis reveals that a normal SER had a good negative predictive power for gross motor development (93%),

personal /social skills (96%), speech and hearing (89%), fine motor coordination (96%), and for the overall developmental quotient or GQ (93%). Therefore a normal SER in infancy predicted normal overall developmental status at 1 year of age.

iii. ABR

The frequency of ABR abnormalities decreased significantly (>50%) in this cohort when compared to the previous study on the predictive value of the ABR.[22] Furthermore, 1 or 2 false positives made it difficult to demonstrate a significant relationship between the ABR findings and the outcome measures. Nonetheless, abnormalities in I-III/I-V interwave latency were associated with neurologic deficits at 1 year of age. Three out of four with increased brainstem conduction had abnormal neurologic exams. Three out of 4 had developmental deficits in several areas, and 2/4 were noted to have low attention spans. There were 3 more subjects with borderline brainstem conduction times, and all 3 had abnormal neurologic exams at 1 year as well. Therefore, interwave abnormalities best predicted neurologic sequelae at 1 year of age.

iv. multi-modality evoked responses (ABR and SER)

Evoked responses were first classified as normal if both tests were normal, or abnormal if the SER or ABR had any abnormal features (i.e. SER: increased latencies or flat response, ABR: increased conduction time, or abnormal

morphology, dispersal or V/I amplitude ratio). Analysis revealed a relationship between evoked response findings and each of the developmental subscores. Normal evoked responses had a negative predictive power and sensitivity of 100% for personal/social skills, speech and hearing, fine motor coordination, and the overall general quotient.Negative predictive power for locomotor development and adaptive and reasoning skills were 92% and 85% respectively. Therefore a normal ABR (i.e. conduction time and waveform amplitude and morphology) and SER were predictive of normal developmental scores in all areas. A similar trend was seen when categorizing ABR abnormalities to include increased interwave latencies only.

By classifying an ABR and SER as normal if waveforms were present and of normal latency (therefore not including amplitude ratios or morphology of waveforms), multi-modality evoked responses were found to be predictive of neurologic status at 1 year of age (Table 6) with a positive predictive power and specificity of 75% and 85%, and a negative predictive power and sensitivity of 92% AND 86% respectively (p<.001). Therefore normal evoked responses (i.e ABR and SER) were associated with a normal neurologic outcome at 1 year with little exception. Both infants with normal evoked responses and neurologic sequelae had mild spastic diplegia. In fact, 1 of the 2 had a borderline I-V interwave latency on the ABR. Abnormal multi-modality evoked responses

predicted neurologic impairment as well.

DISCUSSION

Animal models of hypoxic-ischemic insult have demonstrated that there are characteristic patterns of injury to specific brainstem, cerebellar, thalamic and cortical structures. Human neuropathologic studies have shown that the cochlear nuclei, superior olives, and inferior colliculi (auditory pathway), and the gracile and cuneate nuclei, ventroposterior aspect of the thalamus, and parietal cortex (dorsal column- medial lemniscal pathway) are selectively vulnerable regions.[13-16,24-25] Evoked potentials performed on animals following periods of hypoxia or ischemia show that the ABR and SER components are altered significantly in amplitude and latency by hypoxic ischemic events. The more rostral structures (i.e. generators of N19 in the SER) were most vulnerable to ischemia. Abnormalities in the ABR and SER appear to reflect the extent and evolution of the resultant lesion.[17,26-28]

The integrity of the maturing central nervous system may be compromised by a multitude of prenatal and perinatal circumstances. The subsequent neurodevelopmental outcome in the individual child is often difficult to accurately predict early in life.[25] Evoked potential studies evaluate the functional integrity of the ascending neuraxis, and may therefore prove to be a useful prognostic tool.

Studies have shown that evoked responses have prognostic utility for comatose patients.[29-30] Evoked response abnormalities are common in graduates of the neonatal intensive care unit, and these findings may reflect injury to the maturing brain.[4,31-35]

There has been a growing interest in evoked responses as prognostic tools in high risk newborns. Hecox & Cone (6) investigated the prognostic importance of the ABR in asphyxiated newborns and infants and found that all patients with abnormal V/I amplitude ratios died or were spastic quadriparetic as a result of the asphyxia. However a normal ABR did not ensure a normal outcome. Stockard et al (36) reported that the prognostic power of the ABR increases if the test is done closer to discharge from the neonatal unit. Infants with absent or significanty depressed peaks were severely neurologically impaired on follow-up. Most patients with increased brainstem conduction time had neurologic sequelae as well.

Visual evoked responses (VER) in newborns are technically more difficult to perform and waveforms are more variable and more difficult to interpret reliably. In one study, an abnormal VER that persisted for more than 2 weeks was associated with an abnormal outcome.[37] Whyte et al (38) have shown that serial VERs in asphyxiated full term infants were predictive of clinical status at 6 months of age.

There has been recent interest in the predictive value

of the SER in high risk newborns. Gorke examined 73 infants with a variety of neuromotor problems in infancy. All 19 infants with significantly increased latencies or absent peaks demonstrated handicap after the first year. There were false negatives, however it should be noted that the control group included patients with minor risk factors and slightly abnormal SERs therefore the predictive value of subtle although significant abnormalities could not be determined.[39]

Willis et al (40) studied 10 asphyxiated term newborns serially in infancy using the SER. Patients were assessed blindly by a psychologist and neurologist at a mean age of 20 months. Results showed excellent correlation between SER findings and outcome. All 6 patients with increased latencies of N19 or absent parietal peaks had neurologic sequelae, whereas the 4 patients with 2 or more normal SERs had a normal neurologic outcome. Further studies on a larger cohort are needed to confirm these findings.

Thirty premature infants with abnormal cranial ultrasounds were assessed with SER by Klimach & Cooke (41) at a mean conceptional age of 35 weeks. Twenty-five out of 30 were followed between 6-16 months of age: follow-up assessments were performed on half, and information was derived by questionnaire for 10 patients. All with normal SERs were normal so far in spite of parenchymal lesions picked up on ultrasound. Four patients with abnormal SER

corresponding to the side of the parenchymal lesion had clinical evidence of hemiplegia. Those followed with bilateral SER abnormalities had developmental deficits and 6/7 had neurologic findings as well. In contrast with the previous 2 studies, the negative predictive power for cerebral palsy or developmental delay was 100%, as there were no false negatives. However, this study had diverse follow-up assessment measures that were performed at variable ages. Furthermore, measures of outcome were not performed in a blind fashion. The advantage of this study was that SER testing was carried out in the newborn period.

Willis et al (42) recently evaluated the predictive value of the SER in 39 premature infants with periventricular hemorrhage. As in their previous study on term newborns, they elected not to test infants in the newborn period as waveforms are more difficult to interpret. Neurologic and developmental evaluations were performed in a blind fashion at a mean age of 22 months corrected age. All 15 with abnormal SERs at least on one occasion had abnormal Bayley Motor Scores, and 14/15 had severe neurologic sequelae. However, a normal SER did not ensure a normal outcome. SER abnormalities did not lateralize with the side of the hemorrhage.

Methodological problems in the studies reported to date include inadequate normative data, non-specific testing ages or testing procedures, and no unbiased assessment of outcome. (40,42)Studies by Willis et

al were well designed and yielded important information regarding the predictive power of the SER. False negatives were a problem, however they may have been diminished if SER testing were carried out in the newborn period. Results of our study indicated that several high risk newborns had abnormal SERs initially that normalized by 2 months of age, and subsequently demonstrated mild to moderate neurodevelopmental handicap at 1 year of age.

In a previous study in our laboratory, the ABR performed in the newborn period had a strong positive predictive power and high specificity for neuromotor status at 1 year corrected age. Therefore an abnormal ABR predicted neurologic abnormalities and gross motor delay at 1 year. However there were false negatives, as a normal ABR did not ensure a normal outcome. Therefore the ABR appears to be sensitive to one pattern of injury involving the auditory relay nuclei as well as other structures in the nervous system.[22]

To improve the sensitivity of evoked potentials as a prognostic tool for high risk newborns, the SER was performed together with the ABR so that brainstem as well as more rostral regions of the neuraxis could be evaluated simultaneously. The results of this study show that:

1. An abnormal SER predicts neurologic impairment at 1 year corrected age.

2.   The degree of SER abnormality reflects the degree of neurologic impairment.

3.   A normal SER predicts normal developmental scores at 1 year.

4.   Abnormal brainstem conduction (ABR) correlates with neurologic sequelae.

5.   Normal multi-modality evoked responses (normal ABR and SER) are strongly associated with normal developmental scores with little exception.

6.   Normal central conduction time (ABR and SER) predicts normal neurologic outcome at 1 year of age.

At present, it is difficult to accurately predict before the first year the presence and extent of neurologic handicap in newborns at risk. The results of this study show that evoked responses are a useful adjunct to the clinical and neuroradiologic investigation of newborns at risk for neurodevelopmental sequelae. This study emphasizes the importance of serial evoked response testing in infancy, as the maturational changes early in life appear to reflect the evolution and extent of brain injury. False negatives, which have been a problem for previous studies, appear to be diminished significantly by using multi-modality responses and by testing in the newborn period as well as in infancy.

In summary, multi-modality evoked responses are excellent predictors of neuromotor status at 1 year of age in high risk newborns. Further follow-up of these children to school-age would be of interest in determining the prognostic value of these tests on language, learning and behavioral performance.

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LEGENDS

Figure 1

Experimental design.

Table 1

Recording parameters for evoked response testing

Table 2

Neurodevelopmental risk factors for all newborns

Table 3

2 X 2 table of SER and neurologic status at one year

Table 4

3 X 2 table of the degree of SER abnormality and neurologic status at one year

Table 5

The evolution of all SER abnormalities and subsequent neurodevelopmental findings.

Table 6

2 X 2 table of multi-modality evoked responses and neurologic status at one year.

Experimental Design
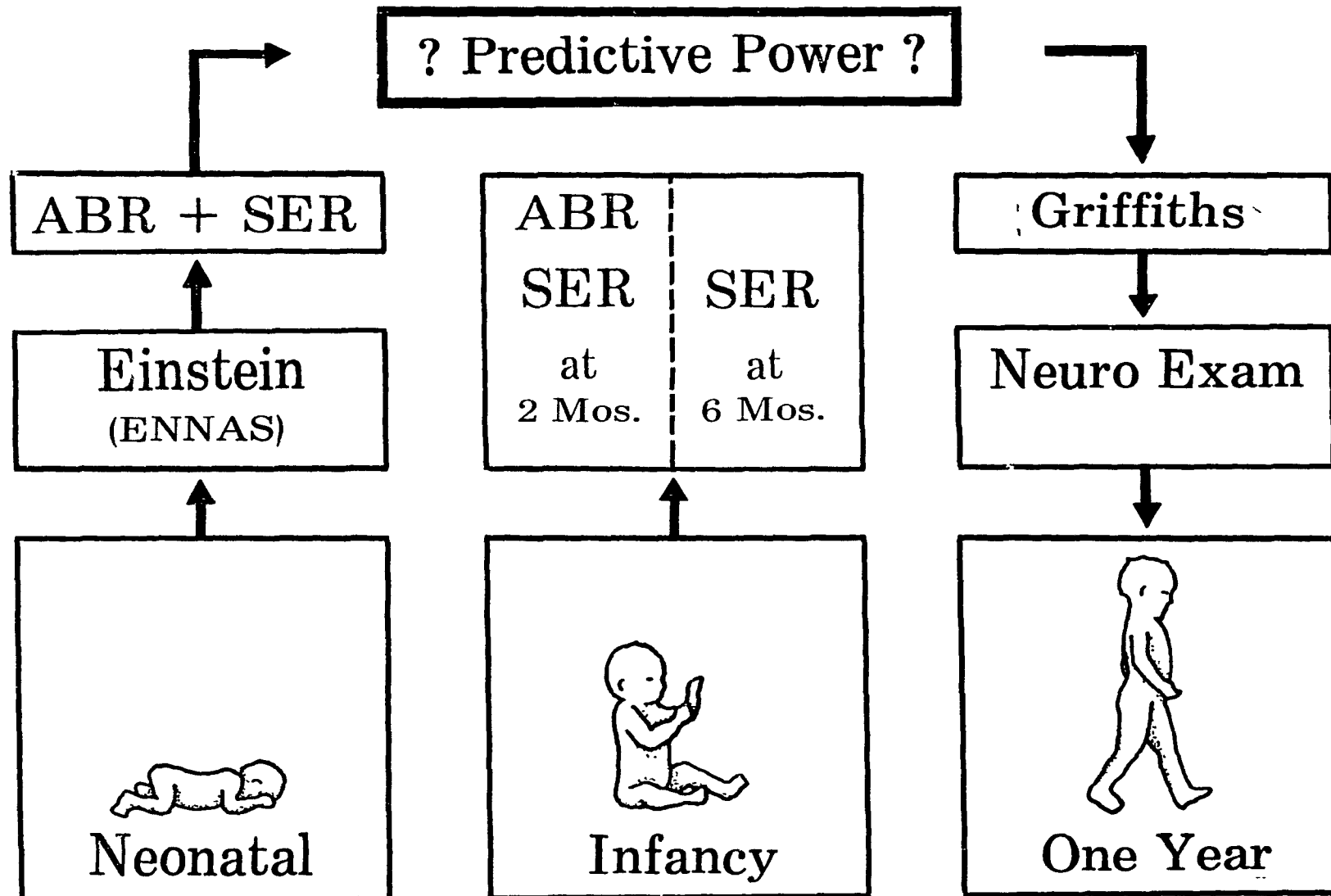
FIGURE 1

Recording Parameters

Test	Montage	Amplification	Filter Setting (Hz)	Sweep (msec)	Vertical Scale	#Responses/ Trial
ABR	Cz-ipsi. ear	100,000x	100-3000	10	x16	1024
SER	Fz-EP Fz-CII Fz-C'c	100,000x	30-3000	50	x4	512

TABLE 1

Neurodevelopmental Risk Factors

Birth Weight (g)	No Asphyxia	Asphyxia (Preterm)	Asphyxia (Full Term)	Total
AGA >1500	19*	5	28	52
AGA <1501	1	6	0	7
SGA	2	1	1	4
Total	22	12	29	63

*Control group

TABLE 2

2x2 Table of SER and Neurological Status at 1 Year

Neurological Examination	SER Abnormal	SER Normal	Total
Abnormal	11	3	14
Normal	3	23	26
Total	14	26	40

p<.001

TABLE 3

3x2 Table of Serial SER and Neurological Status at 1 Year

Neurological Examination	SER Abnormal Persistent	SER Abnormal Improving	SER Normal	Total
Abnormal	4	7	3	14
Normal	0	3	23	26
Total	4	10	26	40

p<.001

TABLE 4

TABLE 5

SER Abnormalities and Neurodevelopmental Outcome

Patient Risk Factors	SER (Parietal Potentials)			Outcome	
	Initial	2 Months	6 Months	Neurologic Exam	Devel. Scores ▲ (<2SD)
I. Persistent/Worsening Responses					
1 **Asphyxia** (Full Term)	Absent N19 bilaterally	--	Absent N19 bilaterally	Spastic quadriplegia	Untestable
2 **Asphyxia*** (Full Term)	Absent N19 bilaterally	Absent N19 bilaterally	*Deceased*	Spastic quadriplegia, No developmental milestones, Died at 4 months *Aspiration pneumonia*	--
3 **Asphyxia** (Full Term)	↑N19, N13-N19 bilaterally	↑N19, N13-N19 bilaterally	Absent N19 bilaterally	Spastic quadriplegia	Untestable
4. **Asphyxia** (Premature) VLBW	Absent N19 unilaterally (R)	?peaks, ↑ latencies (R)	Absent N19 unilaterally (R)	Double hemiplegia R>>L	Global delay
5 **Asphyxia** (Full Term)	Normal	?peaks, ↑ latencies (R)	Absent N19 unilaterally (R)	Right hemiplegia	Normal
II. Improving/Normalizing Responses					
6. **Asphyxia** (Premature) SGA	-- *Not stable medically*	Absent N19 (R) ↑N19, N13-N19 (L)	↑N19, N13-N19 (R), Normal (L)	Spastic diplegia >R	E, GQ
7. **Asphyxia** (Premature) VLBW	↑N19, N13-N19 (R)	Normal (↑N19-P22,R)	Normal	Mild spastic diplegia	Normal
8 **Asphyxia** (Premature) VLBW	↑N19, N13 N19 (L)	Normal	Normal	Normal	E, GQ *Hyperactive*
9. **Asphyxia** (Premature) VLBW	↑N19, N13-N19 bilaterally	Normal	Normal	Normal *Hyperactive*	E *Hyperactive*
10 **Asphyxia** (Premature)	↑N19, N13-N19 bilaterally	Normal	Normal	Mild spastic diplegia>R *Hyperactive*	B, C, E *Hyperactive*
11. **Asphyxia** (Premature)	Absent N19 bilaterally	Normal	Normal	Mild spastic quadriplegia, Macrocephaly *shunted*, Motor delay	--
12 **Asphyxia** (Full Term)	↑N19, N13-N19 (L)	Normal (N19 P22,L)	Normal	Normal	Normal *Hyperactive*
13. **Asphyxia** (Full Term)	?peaks (R), ↑latencies bilaterally	↑ N13-N19 bilaterally	Normal	Mild right hemiplegia	Normal *Left preference*
14. **SGA**	↑N19, N13 N19 (R)	?peaks (R) (↑N19 P22, L)	Normal (↑N19-P22, R)	Microcephaly	A, B, C, E, GQ
15 **Asphyxia** (Full Term)	Absent (L) ?peaks (R)	L-normal ?peaks (R)	L-normal R unco-op	Microcephaly, Deaf	A

▲ Developmental scores: A Locomotor, B Personal/social, C Speech/hearing, D Eye hand co-ordination, E Adaptive & reasoning skills, GQ General quotient

* Patient died in infancy, therefore was not included in chi square tables

↑ Increased latencies

? Questionable, low amplitude peaks

R Right, L Left (median nerve stimulated)

2x2 Table of Multi-Modality Evoked Responses and Neurological Status at 1 Year

| Neurological | ABR and SER | | |
Examination	Abnormal*	Normal	Total
Abnormal	12	2	14
Normal	4	22	26
Total	16	24	40

*Abnormal SER and/or increased brainstem conduction in ABR
p<.001

TABLE 6

ACKNOWLEDGEMENTS

SUMMARY

Studies examining the clinical utility of evoked responses in pediatrics have focused primarily on the ABR, particularly when considering the possible applications to newborns and young infants. There has been growing interest in exploring the potential value of utilizing SER as a diagnostic test for a number of clinical conditions. The DISCUSSION will summarize the literature on the maturational changes that characterize the SER in healthy newborns and children. Findings in high risk newborns will be described as well. The rationale for using multi-modality evoked responses as predictors of outcome and the current literature on auditory, visual and somatosensory evoked potentials as prognostic tests in high risk newborns are presented. The results of the studies that comprise this thesis are reviewed in light of the existing literature.

SOMATOSENSORY EVOKED RESPONSES (SER) IN HEALTHY AND HIGH RISK NEWBORNS

i.) SERs in children: developmental changes

There have been several studies, particularly in the mid-80's, describing the maturational changes that are characteristic of somatosensory evoked responses (SER) in children. Generally the median nerve is stimulated (Bartel et al, 1987; Hashimoto et al, 1983; Lauffer & Wenzel, 1986; Luders, 1970; Nishimura et al, 1986; Sitzoglou & Fotiou, 1985), however SER following electrical stimulation of the posterior tibial nerve has been described in children as well (Cadilhac et al, 1985; Gilmore et al, 1985; Zhu et al, 1986). Cracco and Cracco (1982) reported on spinal SER recordings with surface electrodes placed along the spine.

A variety of stimulating and recording parameters are described in the literature and waveform nomenclatures are inconsistent. For example, the cortical potential generated over the contralateral parietal scalp following median nerve stimulation is referred to as N1, N19 or N20. The positive peak immediately following this negative deflection is labelled as P1, P22 or P25. Furthermore these studies vary widely in the number of subjects tested (up to 90) and the age group studied. Several studies look at a range of ages beginning at a few days of life to mid-childhood or adolescence (Bartel et al, 1987; Cadilhac et al, 1985; Gilmore et al, 1985; Hashimoto et al, 1983; Lauffer &

Wenzel, 1986; Nishimura et al, 1986; Sitzoglou & Fotiou, 1985; Zhu et al, 1986), whereas earlier studies delineate primarily SER findings in adults and the elderly (Dorfman & Bosley, 1979; Hume et al, 1982; Luders, 1970).

Despite the lack of methodological standardization in the literature on SERs in children and adults, the conclusions are quite similar. The peripheral potentials mature before central potentials, and the upper extremity matures before the lower extremity. Therefore upper extremity recordings are more constant and reliable in young infants, and the potentials generated over the brachial plexus and cervical spine are more easily identifiable in newborns than the parietal potentials (Cadilhac et al, 1985; Zhu et al, 1986). Absolute latencies of N19 (also referred to as N20, N1) decrease with increasing age until about 2-5 years, then the latencies increase with increasing body length (Bartel et al, 1987; Cadilhac et al, 1985; Hashimoto et al, 1983; Zhu et al, 1986). From adolescence to adulthood there is little change in absolute latencies of parietal potentials (Hume et al, 1982). Central conduction time can be estimated by measuring the interwave latency between N13 (cervical potential) and N19 (parietal potential). Central conduction time decreases as a function of increasing age, particularly in early childhood (Bartel et al, 1987; Sitzoglou & Fotiou, 1985) with adult values obtained at about 8-10 years (Hashimoto et al, 1983; Lauffer & Wenzel,

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1986; Tomita et al, 1986) and then increases abruptly between the fifth and sixth decades whereupon it stabilizes (Dorfman & Bosley, 1979; Hume et al, 1982). Zhu et al (1986) found that the difference between the onset and peak latencies which is referred to as the ascending time of the parietal potential consistently decreases with advancing age. Therefore, there is an inverse relationship between waveform duration and age (Cadilhac et al, 1985). Amplitude and morphology of the SER waveforms show less clearcut correlation with age, however the amplitude of parietal potentials generally follow a U-shaped curve with amplitudes decreasing between early (10-30) and mid-adulthood (40's) (Cadilhac et al, 1985; Hume et al, 1982; Luders, 1970). SER recordings following stimulation of the posterior tibial or peroneal nerve produce responses that are more variable in morphology and latency, particularly in the younger age groups (Cadilhac et al, 1985), and the relationship between age and height are less well defined (Gilmore et al, 1985).

In summary, the developmental changes in SERs in children include progressive shortening of central conduction time and enlargement of amplitude of potentials generated over parietal scalp. These maturational changes likely reflect myelination and increased synaptic efficiency and synchrony of firing of the ascending somatosensory pathways (Lauffer & Wenzel, 1986, Sitzoglou & Fotiou, 1985; Tomita et al, 1986). SERs in children provide

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a unique opportunity to evaluate objectively both peripheral and central sensory pathways, and may be used as an index of cerebral maturation (Bartel et al, 1987; Nishimura et al, 1986).

ii.) <u>SERs in newborns</u>

At present, there are few reported clinical studies of SERs in neonates. Stimulating and recording parameters are highly variable (i.e. nerve stimulated, type of stimulus, rate and number of stimulations, montage), therefore it is difficult to compare normative data between laboratories. Different waveforms (both short and long latency) have been identified, using a variety of nomenclatures (Desmedt & Manil, 1970; Hrbek et al, 1973; Pratt et al, 1981; Willis et al, 1984). SER recordings in newborns are usually elicited following stimulation of the median nerve. The advantage of using an electrical stimulus is that threshold is readily and objectively determined by the production of a muscle twitch (Willis et al, 1984). More recently, investigators have looked at SER following bilateral electrical stimulation of the posterior tibial nerve or the peroneal nerve (Cullity et al, 1976; Gilmore et al, 1987). Peripheral responses are readily identifiable however P55 (the parietal potential from lower extremity stimulation) has variable presence and latency in the newborn (Gilmore et al, 1987). Mechanical stimulators such as a moving coil vibrator or tendon tapping have been of limited value in

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newborns as it is difficult to identify parietal potentials, however this approach may have potential value in the identification of peripheral nerve lesions (Hrbek et al, 1969; Pratt et al, 1981).

A peripheral potential is important to obtain as its presence ensures that an adequate stimulus has been applied to the peripheral nerve and it further demonstrates an intact pathway distal to root entry into the spinal cord (Klimach & Cooke, 1988a). The potentials generated at Erb's point (or popliteal fossa) and over the cervical vertebrae (or lumbar vertebrae) are readily identifiable and are reliably obtained in all newborns (Gilmore et al, 1987; Laureau et al, 1988). It is generally agreed that the parietal scalp contralateral to the stimulated nerve is the best scalp derivation however many other montages are used as well (Willis et al, 1984). The parietal potential (N1, N19 or N20) in newborns is generally of very low amplitude and dispersed (Klimach & Cooke, 1988a; Laureau et al, 1988; Willis et al, 1984). It is occasionally not detectable in healthy newborns (detected in 50%: Blair 1971; 2/3: Willis et al 1984; 85%: Laureau et al 1988; 90%: Klimach & Cooke 1988a).

Several of the earlier investigations on SERs in newborns described the large slow negative response seen in the long latency SER. The early cortical components appear to be more prominent in wakefulness or irregular sleep whereas the later components are larger with regular sleep

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(Hrbek et al, 1969). Maturational changes of the somatosensory pathway in infancy have been described in several studies following electrical stimulation of the median nerve primarily (Blair, 1971; Cullity et al, 1976; Desmedt & Manil, 1970; Hrbek et al, 1968; Hrbek et al, 1973; Klimach & Cooke, 1988a; Laureau et al, 1988; Pratt et al, 1981; Willis et al, 1984). These studies show that with increasing age, absolute and interwave latencies decrease and amplitudes increase.

In the first article presented in this thesis, "a longitudinal study of short latency somatosensory evoked responses in healthy newborns and infants", an easy and reliable method of performing SERs in infants was delineated. We studied 18 healthy full term newborns in the first week of life, with gestational ages ranging from 37 to 42 weeks. Serial testing at 2-3 months and 6-7 months of age was carried out to determine the maturational changes of the SER in infancy. Stimulating and recording techniques were similar to those described by Willis et al (1984), as the responses were reliable and readily reproducible using this approach. Parietal potentials were clearly identifiable in the majority (85%) of newborns which contrasted with findings by Blair (1971) and Willis et al (1984) where potentials were obtained in 50% and 2/3 of cases respectively. Our findings are comparable to those of Klimach & Cooke (1988a) who report that 90% of newborns had identifiable N19 peaks.

In our study, we attempted to control for the possible effects of state of consciousness on the parietal potentials. Newborns were tested when drowsy or asleep and infants were tested when awake. Infants who fell asleep during testing demonstrated a decrease in the amplitude of the N19 peak as well as a slight prolongation of the P22 latency. These alterations in waveform morphology during sleep recordings reinforce previous reports by Hrbek et al (1969) and Desmedt & Manil (1970).

Relative amplitudes or amplitude ratios between N13 and N19 as well as dispersal ratios (height of the waveform divided by its base) were established to quantify morphological characteristics of the N19-P22 waveform. Dramatic changes in these ratios were noted between the neonatal period and 2 months of age, reflecting significant maturational changes in the central nervous system in early infancy. These rapid changes in the ratio values resulted from an increase in amplitude of N19 as well as a markedly diminished duration and dispersal of the waveform.

The peripheral Erb's point potential (EP) as well as N13 (generated over C II) were clearly identifiable in all newborns tested, and the latencies decreased marginally in infancy. In contrast, the parietal potential decreased significantly in latency and variability over the first 6 months of life, and was more easily recognizable, being of larger amplitude and shorter duration. These findings likely reflect progressive myelination and increased synaptic

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efficiency predominantly in the central sensory pathway. These maturational changes parallel the findings of histopathologic investigations of the immature nervous system (Gilles et al, 1983; Yakovlev & Lecours, 1967).

In the second article: "the effect of gestational age on the short latency somatosensory evoked response performed at term", we hoped to establish that normative data from healthy full term infants can be applied clinically to premature infants tested at term. The literature clearly demonstrates that latency measurements for the ABR decrease as a function of conceptional age (defined as gestational age plus postnatal age), and that developmental changes in conduction are independent of intrauterine or extrauterine environment (Fawer & Dubowitz, 1982; Krumholz et al, 1985· Salamy, 1984). This has been challenged primarily by behavioral studies that contend that neurologic development may be accelerated by early exposure to the extrauterine environment (Amiel Tison, 1980; Gilmore et al, 1987; Gould et al, 1972). Therefore we tested 9 low risk premature infants at term (37-42 weeks conceptional age) with the SER and compared their findings with those of healthy full term infants. The results clearly indicate that both ABR and SER latency measurements were similar for infants matched for conceptional age, whereas conduction time was significantly discrepant for infants matched for chronological age. Furthermore, visual inspection of the SER parietal potential in premature and full term infants

demonstrates that infants of similar conceptional age have remarkably similar morphologic characteristics. Therefore the rate of myelination appears to be independent of premature birth (i.e early extrauterine exposure).

iii.) SERs in high risk newborns

The SER is becoming increasingly recognized as a useful diagnostic tool in newborns. This noninvasive test examines the peripheral and central ascending pathways, and is especially useful in young children, where clinical examination of the sensory system is difficult and often unreliable. This technique allows you to objectively evaluate the conduction along ascending sensory pathways, and to follow developmental changes in the nervous system such as loss or recovery of function (Gilmore, 1989; Rotteveel et al, 1982). Rotteveel et al (1982) reported a very high percentage of abnormal SERs in retarded infants (0- 2 1/2 years) with a variety of neurologic disorders such as chromosomal aberrations, degenerative diseases, and cerebral dysgenesis. Several other studies confirm the high prevalence of SER abnormalities in young children with neurodegenerative disorders (Gilmore, 1989). There have been several reports of SER recordings in newborns at high risk for neurologic sequelae as a result of pre or perinatal injury to the brain. Hrbek et al (1977) performed long latency SERs on 57 asphyxiated newborns, primarily in the first week of life. The long latency components (which are

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generally several hundred msec) were noted to be of low amplitude, absent or of increased latency in 65% of patients. Those with persistent abnormalities had clinical evidence of brain injury. The methodology in this study was not clearly defined, therefore precise interpretation of the findings is difficult. More recent reports on SER findings in both normal and high risk populations focus predominantly on the more reliable short latency N20 (N19) component, as opposed to the subsequent longer latency components that these authors describe.

In one study, ABR and SER performed on 10 asphyxiated babies at 3 months of age revealed normal or slightly prolonged ABRs, however no cortical responses were elicited in the SER. All infants had tone abnormalities, infantile spasms and neuroradiologic evidence of severe leucomalacia and cortical atrophy (Lutschg et al, 1983a).

Willis et al (1987) recorded SERs in 10 term infants with perinatal asphyxia at 2-6 months of age. Abnormalities included increased latencies and absent peaks of the parietal potential. Both improvement or persistence of abnormalities were documented. Absent potentials were seen in half of the subjects. Those that normalized had mild to moderate developmental deficits on follow-up whereas persistently absent potentials were associated with a severe outcome.

Ultrasounds are diagnostically useful in identifying structural lesions whereas evoked potentials are used to

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evaluate the functional integrity of neural pathways. Klimach & Cooke (1988b) pre-selected a group of high risk newborns with abnormal cranial ultrasound. Eight out of 30 also had neonatal seizures. The mean gestational age of the group was 30.5 weeks (range 25-40) and the mean age at testing was 35.3 weeks conceptional age (range 30-44). SERs following median nerve stimulation showed that N19 peak latencies were significantly different (p<.001) between infants with normal versus abnormal ultrasounds. Twenty-one out of 30 infants with abnormal ultrasounds had increased latencies, and 2 had absent potentials unilaterally or bilaterally. Of the 2 infants with absent peaks, 1 was hypotonic and 1 was neurologically normal in the newborn period. SERs were repeated in 13 patients, and 7 had normalization of recordings. One child had progressive worsening of latencies and this child subsequently died in infancy.

As part of a longitudinal study in our laboratory, SERs were performed on high risk as well as healthy newborns. In article 3: "Somatosensory evoked response abnormalities in high-risk newborns", 34 high risk newborns were tested in the newborn period and again in infancy with the SER. Findings were compared to those of healthy term infants matched for conceptional age. Abnormalities documented in the high risk group included increased absolute (N19, P22) and interwave (N13-N19, N19-P22) latencies, and absent parietal potentials. Serial testing

revealed that normalization of prolonged conduction time was associated with mild neurologic handicap whereas persistently absent potentials were seen in children with severe neurological impairment in infancy. Unilateral abnormalities, or abnormalities that were more prevalent on one side than the other, correlated with subsequent lateralization of neurologic deficits to the corresponding side. In this study, CT and ultrasound studies performed on these patients in the newborn period were scored in a blind fashion by a neuroradiologist. No significant relationship between the SER and radiologic investigations were noted. In summary, approximately 1/3 of patients had SER abnormalities, and the extent and evolution of the abnormality appeared to reflect subsequent neurologic sequelae in the first months of life (Majnemer et al, 1987).

In conclusion, there have been a few recent studies on SERs in high risk neonates, notably on asphyxiated newborns. When examining SER findings in high risk newborns, results show a significant percentage of abnormalities in the parietal potential with normal peripheral potentials. Abnormalities include increased latencies (both absolute and interwave), and low amplitude or absent peaks. Abnormalities may be unilateral or bilateral, and may persist or improve on follow-up testing in infancy.

i.) <u>The prognostic value of evoked potentials in ICU</u> <u>populations</u>

Several recent reports on the utility of evoked potentials in predicting outcome of comatose patients have yielded promising findings. In a study by Frank et al (1985), the absence of the SER parietal potential with preservation of the ABR in 5 children with hypoxic insults correlated with loss of cortical function and preservaiton of brainstem function. The finding that an absent N19 peak in the SER predicts chronic vegetative state or death was similarly reported by Zegers de Beyl & Brunko (1986) in a group of 50 adults. The authors emphasize that this correlation does not appear to hold true for traumatic brain injury, as absent peaks may normalize over time with concomitent recovery of cognitive skills. Therefore the predictive value is dependent on the pathophysiology of the coma.

When comparing the predictive value of the ABR and SER, the SER appears to be more effective in predicting outcome (De Meirleir & Taylor, 1987; Greenberg et al, 1982 ; Lutschg et al, 1983b). De Meirleir & Taylor (1987) performed SERs on 73 comatose children upon admission to the ICU. Twenty seven patients died, and none had a normal SER. All 14 children with a normal outcome had normal SERs or interwave abnormalities that resolved on serial testing. Utility of

this test did not appear to vary for etiology. In a previous study (De Meirleir & Taylor, 1986), the ABR was not found to be effective in predicting outcome, althought very abnormal recordings were associated with a poor prognosis. Greenberg et al (1982) reported that evoked potentials had 91% correct predictions with no false positives in 109 patients (5-70 years) post severe head injury. There was no significant difference between the predictive accuracy of the SER (analyzed short and long latency components) and multimodality evoked potentials, and the severity of the SER abnormality correlated with mortality. Evoked potentials were more predictive of outcome than CT, intracranial pressure, the Glascow Coma Scale, and the clinical exam in this cohort of patients. In a retrospective study on 43 comatose children with hypoxic-ischemic injury (6 months-15 years), a loss of ABR components was associated primarily with death or neurologic sequelae (Lutschg et al, 1983b) . No patient that either died or suffered neurologic deficits had normal ABR and SER, and those with normal outcomes had normal evoked responses or responses that normalized over time, confirming the findings of De Meirleir & Taylor (1987). Slowing of axonal conduction as a result of cerebral edema was thought to contribute to an increased central conduction time of the SER (N13-N19) which improved over time. Structural changes such as neuronal necrosis or secondary demyelination could conceivably cause either decreased amplitude of waveforms or

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prolongation of central conduction time. The authors found the ABR to be more resistent to hypoxic insult than the SER (Lutschg et al, 1983b).

In conclusion, evoked potentials are useful prognostic tools for comatose patients, yielding valuable information regarding the topography and evolution of lesions. The central conduction time in the ABR and short latency SER are unaffected by barbiturates and therefore give important supplementary information regarding brain function. In patients who are brain dead, the SER N20 peaks are absent bilaterally, however the N13 may still be present. The ABR is either flat or wave I alone may be identified (Kaga et al, 1985; Lutschg et al, 1983b; Starr, 1976). The clinician must be cautious about the use of evoked potentials in determining brain death, as the evoked response abnormalities mentioned above are associated but not exclusive to brain death. For example with the ABR, deafness, technical artifact or extensive brainstem lesions could contribute to a flat ABR or loss of waves II-V (Chiappa, 1983).

ii.) Rationale for use in the neonatal ICU

Periods of hypoxia, ischemia, increased intracranial pressure, alterations in cerebral blood flow and blood pressure in the immature brain may result in permanent injury to the nervous system. Animal models of hypoxic-ischemic insult have demonstrated that there are

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characteristic patterns of injury to specific brainstem, cerebellar, thalamic, and cortical structures. The character of the insult determines the extent and location of the subsequent injury. Experimental and human neuropathologic studies have shown that the cochlear nuclei, superior olives and inferior colliculi as well as the gracile and cuneate nuclei, ventroposteriolateral thalamus and parietal cortex are among regions that are selectively vulnerable to anoxic-ischemic insult in the maturing nervous system (Hall, 1964; Leech & Alvord, 1977; Myers, 1975; Ranck & Windle, 1959; Volpe, 1987).

Evoked potentials are non-invasive electrophysiologic tests that measure the functional integrity of the ascending neuraxis. It is feasible that damage to structures along the auditory and somatosensory pathways as a result of hypoxia and/or ischemia would be revealed by abnormal auditory brainstem and somatosensory evoked responses. This has been supported by evoked potential studies on animals prior to and following hypoxia or ischemia. Sohmer et al (1983) found that the ABR was resistent to change following hypoxia in cats, and only became depressed in amplitude if the mean arterial pressure decreased. The relationship between SER and cerebral oxygen consumption and cerebral blood flow was examined in 10 dogs by McPherson et al (1986). The results of this study showed that the latencies of N19 and P22 increased with cerebral oxygen deprivation and there was a dramatic diminution of peak amplitudes.

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There was a normalization of SER as the oxygen became available again and the brain was able to utilize the oxygen. The authors stipulate that the SER may be potentially useful in evaluating the efficacy of cerebral oxygen delivery in brain injured patients.

Ischemia, induced by manipulation of cerebral perfusion pressure (decreasing mean arterial pressure or increasing intracranial pressure), will induce changes in amplitude and latency in the ABR in cats (Sohmer et al, 1983) and SER (Nagao et al, 1979). Following unilateral occlusion of the middle cerebral artery, severe ischemia in the region of the ectosylvian gyrus was associated with a loss of the SER cortical components in the experimental hemisphere, and a diminution of amplitudes and increase in latencies in the control hemisphere. If the clip was removed from the artery after 2 hours, the waveforms failed to reappear, despite restoration of blood flow (Coyer et al, 1986). In a similar study on 13 baboons, cortical SER potentials were noted to decrease in amplitude during cerebral ischemia following occlusion of the ipsilateral middle cerebral artery. Central conduction time was found to increase with ischemia as well (Branston et al, 1984). In this experiment, depth electrodes were placed in the ventroposteriorlateral aspect of the thalamus, the medial lemniscus in the brain stem, and in the cerebral cortex. This study revealed a differential ischemic sensitivity along the neuraxis, with the rostral portion being more sensitive to local ischemia and systemic

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hypotension, whereas the brainstem was most resilient.

Increased intracranial pressure will also alter the amplitude and latency of ABR and SER components. The higher centers were found to be more susceptible to raised pressures than lower centers, reinforcing the findings of Branston et al (1984) (Matsuura et al, 1986; Nagao et al, 1979).

The results of the above studies indicate that the ABR and SER are sensitive to hypoxic-ischemic insults, and the cortical structures appear to be particularly vulnerable. Therefore one could hypothesize that newborns that have suffered hypoxic-ischemic injury may demonstrate abnormal evoked responses and these abnormalities may reflect the extent and location of the resultant lesion(s). Furthermore, repeat testing in infancy may elucidate the evolution of the injury to the brain.

One must first establish that evoked response abnormalities are characteristic of newborns who may have suffered a hypoxic-ischemic injury. Numerous studies of auditory brainstem and to a lesser extent, somatosensory and visual evoked potentials in high risk newborns have exhibited a high incidence of abnormal responses. Abnormal absolute and interwave latencies are commonly documented in high risk infants, particularly those with apneic or respiratory distress syndrome, intraventricular hemorrhage, neurologic signs such as hypertonia or hypotonia, and infants of very low birthweight, and those with

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hyperbilirubinemia or asphyxia (Fawer et al, 1983; Gorney, 1986; Ito, 1984; Kileny et al, 1980; Mochizuki et al, 1986; Murray, 1988; Streletz et al, 1986). For example, when examining the performance of high risk newborns on ABR testing, 89% of asphyxiated infants in one study had some abnormality (threshold elevations primarily), and the extent and evolution of the abnormality appeared to reflect either worsening or improving clinical course (Yasuhara et al, 1986). Lutschg et al (1980) reported that 22 out of 40 asphyxiated newborns with neurologic abnormalities had predominantly prolonged latencies on the ABR. The neuropathologic findings on the 8 patients who died correlated with the extent and location of the abnormalities of the ABR components. Infants that are small for gestational age also have an increased incidence of prolonged central transmission time, when compared to an age matched control group with birthweights appropriate for gestational age (Saintonge et al, 1986). Sixty-one very low birthweight infants with intracranial hemorrhage were tested with the ABR by Semmler et al (1986), and the severity of the hemorrhage was associated with the degree of abnormality of waves III and V latency, and the authors contribute this to the proximity of the site of ventricular bleeding to the inferior colliculus. Similarly, central conduction and morphological abnormalities are common in SERs or visual evoked responses (VER) performed on this population (Hakamada et al, 1981; Hrbek et al, 1977;

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Klimach & Cooke, 1988b; Majnemer et al, 1987; Willis et al, 1987).

Healthy and high risk infants follow distinct developmental curves on serial ABR testing in infancy. For example, peak amplitude trajectories progressively diverge during the latter part of the first year, as the amplitudes of the healthy newborns increase progressively whereas the amplitudes in the high risk group increase marginally and then plateau (Salamy et al, 1980). This study suggests that it may be useful to perform serial evoked response testing in high risk newborns.

It is difficult to compare the findings of these studies on evoked potentials in high risk newborns, as diverse definitions of "high risk" as well as different evoked response measures and technical parameters are used. Often an appropriate control group is not included. Nonetheless, abnormal evoked potentials are prevalent in high risk newborns and these abnormalities may reflect anoxic-ischemic injury to the maturing brain.

There are few diagnostic tools that directly measure neurologic function and maturation. CT scan and ultrasound reveal structural damage and provide some correlation with outcome (Adsett et al, 1985; Bokzynski et al, 1988; Calvert et al, 1986; DeVries et al, 1985). There has been a growing interest in evaluating the utility of evoked potentials as diagnostic and prognostic tools in the NICU. This test may prove to be useful in 1)monitoring development of the

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central nervous system 2)the early identification of those patients that need therapeutic intervention and in 3)predicting outcome (Murray, 1988). Few longitudinal studies that examine the prognostic importance of this electrophysiologic procedure have been reported thus far in the literature.

iii.)ABR as a predictor

Animal lesion and depth-electrode experiments, as well as human clinical and neuropathological correlations, have demonstrated that the ABR accurately localizes injury to the auditory relay nuclei (Buchwald and Huang, 1975; Chiappa, 1983; Hecox et al, 1981; Oh et al, 1981, Starr, 1975; Starr and Achor, 1975). This test does not distinguish etiological factors, but it does provide valuable information on the functional integrity of the brainstem that is difficult to obtain otherwise (Salamy, 1984; Starr, 1984).

Hecox & Cone (1981) investigated the prognostic importance of the ABR after asphyxia in the perinatal period or in early childhood (birth to 18 months of age) in 126 infants. Twenty-one had abnormal V/I amplitude ratios less than 0.5, and all 21 had spastic quadriparesis or died as a result of the asphyxia. Therefore small wave V amplitudes relative to wave I indicated a poor prognosis without exception. However, normal ratios > 0.5 did not guarantee a favorable outcome. Clinical evidence of brainstem dysfunction did not correlate with ABR abnormalities.

Furthermore, there was a poor correlation between the severity of neurological impairment on clinical examination and outcome.

Stockard et al (1983) attempted to correlate neonatal ABR findings with clinical outcome for 74 infants with a variety of perinatal insults. They found no constant relationship between the ABR and severe brain damage, although the prognostic power of the test increased if it was performed several weeks after the perinatal injury. Thirteen of 14 infants with absent later waveforms (III to V) or with significantly depressed wave V amplitudes were severely neurologically impaired at follow-up. The ABRs of 17 patients showed persistence of prolonged interwave latencies, and only four of the 17 were normal at 18 months to four years of age.

Streletz and colleagues (1984) compared I to V interwave latencies of 41 high risk noenates with those of a low risk group of newborns from an intensive care unit with similar conceptional ages. Prolonged interwave latencies correlated poorly with Bayley Scale scores at 18 to 24 months of age. Perhaps better correlations would have been obtained had they used a control group from a well-baby nursery.

In a prospective study from our laboratory (Majnemer et al, 1988), the utility of the ABR as a prognostic tool was examined. Very low birthweight, small for gestational age, and particularly asphyxiated neonates

demonstrated abnormalities in their neonatal ABRs, and at one year these abnormalities best predicted motor outcome. Prolonged conduction time (I-III and/or I-V) predicted gross motor delay, and all high risk infants with increased brainstem conduction had abnormal neurological findings at one year. Very dispersed waveforms and abnormal V/I amplitudes ratios also predicted neurological impairment at one year. All these ABR characteristics showed very high specificity, in that neonates with normal neurological outcomes had normal neonatal ABRs. However, there were false negatives; approximately half the high risk infants with abnormal neurodevelopmental findings at one year had normal neonatal ABRs. It should be noted that the neurological manifestations of this group were primarily spastic diplegia or hemiplegia, suggesting underlying pathology involving the cerebral hemispheres. Animal and human neuropathological experiments have provided evidence for the existence of many patterns of anoxic-ischemic injury to the central nervous system (Volpe, 1987). In view of the findings of this study (Majnemer et al, 1988), the ABR appears to be sensitive to one pattern of injury involving the auditory relay nuclei, as well as other cortical and subcortical structures. The high risk group most vulnerable to this pattern of insult were asphyxiated neonates delivered near term. However, there are other patterns of anoxic-ischemic injury that may not significantly involve the auditory relay nuclei. For these

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patients the ABR could be normal, although their development may not be, which could explain our false negative results.

False negatives need to be diminished to maximize the sensitivity of evoked response testing as a prognostic tool in the NICU. Examination of other sensory pathways using multi-modality evoked potentials may enhance the predictive power of this objective electrophysiologic test in neonates at risk for neurodevelopmental sequelae.

iv.)VER as a predictor

There have been a few reports on normal values for visual evoked potentials (VEP or VER) in newborns. Because of the difficulty of visual fixation onto a point in a pattern shift stimulus with this population, Chin et al (1985) have used light emitting diode goggles to produce a VER in 40 neurologically normal neonates ranging from 23-42 weeks gestational age. In older children and adults, the strobe light photostimulators provide greater variation in evoked response measures and appear to be less sensitive than pattern shift photostimulators in detecting conduction defects (Chiappa, 1983), and therefore are not routinely used clinically Nonetheless, with the goggles, VERs are obtainable and replicable in neonates greater than 23 weeks conceptional age and characteristically appear as a slow negative peak ($\bar{X}$= 308 + 21 msec). This negative peak does not alter significantly in latency from 24 weeks until term, however a postivie peak appearing at about 220 msec ± 22 is

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consistently seen only in full term infants (> 36 weeks gestational age) (Chin et al, 1985). Basilar dendrites in the visual cortex mature early, before 32 weeks gestational age and the consistency of N2 (N300) latency may be reflecting this. Conversely, apical dendrites mature dramatically in the last months of gestation, and this may be represented by the variable appearance of the P2 (P200) peak (Chin et al, 1985; Taylor et al, 1987). A comparison of VER findings in cross-sectional versus longitudinal data suggests that waveforms appear to emerge earlier in the latter, suggesting that the visual cortex matures earlier when exposed to the extrauterine environment (Taylor et al, 1987). The authors concede that there is a problem with waveform identification as there are many more bifid peaks as the infant matures and therefore interpretation (i.e. waveform identification) is more variable. For example, what these authors refer to as a bifid P200 may be interpreted as earlier positive and negative peaks by others. Normative data in the literature is markedly variable and this is likely due to differing methodologies in evoked response testing and interpretation. Furthermore, the state of arousal and the possible effects of medications are generally not controlled for in studies that have established normative data for newborns.

VERs in asphyxiated newborns have demonstrated a high abnormality rate, and an evoked response risk score was found to correlate with the degree of asphyxia (Hrbek et al,

1977). The investigators stress the importance of differentiating transient versus persistent abnormalities. Persistently abnormal VERs (> 2 weeks) were associated with an abnormal outcome in a second study examining the evolution of VERs in infants with a variety of perinatal disorders. There were false negatives (28.6%) and false positives (30%). Furthermore, the abnormalities were not clearly defined, scoring did not appear to be done in a blind fashion, follow-up was not consistent, and the "control" group included high risk newborns that appeared to be developing normally (Hakamada et al, 1981).

Serial VERs in 25 term infants with documented birth asphyxia were found to be predictive of outcome at 6 months of age. Eight out of 9 infants with normal or mildly abnormal VERs were neurodevelopmentally normal at 6 months, whereas infants with prolonged absence of peaks (> 1 week) or abnormal waveforms either died (N=9) or were globally delayed (N=7) at 3-6 months of age (Whyte et al, 1986). Although this study is promising regarding the prognostic value of serial VERs in asphyxiated newborns, outcome determination at 6 months may be somewhat premature. Furtheremore, it was not clear whether or not the examiner at 6 months was aware of the VER findings. Further prospective studies, with an age-matched control group, and blind evaluation of outcome are needed to determine the predictive validity of this electrophysiologic technique in both premature and full term high risk newborns.

v.) <u>SER as a predictor</u>

Several studies have established that SER abnormalities are common in high risk newborns. Furthermore, persistent abnormalities appear to correlate with clinical evidence of brain injury (Hrbek et al, 1977; Lutschg et al, 1983a; Majnemer et al, 1987). In a study on SERs in 43 children with localized motor deficits as a result of perinatal anoxic-ischemic injury, the SER was more accurate than the EEG in localizing and lateralizing the lesion. The authors suggest that this test may be useful in the early diagnosis of brain damage (Laget et al, 1976).

In light of the experimental work that has demonstrated that structures along the somatosensory pathway are selectively vulnerable to hypoxic-ischemic insult (Moore, 1986; Myers, 1975; Ranck & Windle, 1959), and that hypoxia and/or ischemia may cause alterations in the SER potentials (Coyer et al, 1986; McPherson et al, 1986; Nagao et al, 1979; Sohmer et al, 1983), the SER may prove to be a valuable predictor of outcome in high risk newborns.

In the past 3 years, a few studies have reported on the predictive value of the SER Gorke (1986) investigated the prognostic value of the SER in 73 infants with a variety of perinatal and postnatal problems and abnormal development when first assessed (1-10 months of age). Forty-seven infants with minor perinatal risk factors and normal development formed the control group. All 19 infants with significantly increased (> 2 sigma variation) N1 (i.e. N19)

peak latencies or absent potentials demonstrated handicap after the first year of life (11-36 months, median: 13.5 months). Impairments included psychomotor retardation (N=6), cerebral palsy (N=15), degenerative (N=4) and metabolic (N=3) diseases of the central nervous system. Gorke concluded that the SER is valuable as an early indicator of severe motor impairment. There were false negatives, and this may reflect that areas other than the somatosensory pathway may be impaired. In Gorke's study, patients were assessed because of early evidence of neurologic impairment. The experimental group included many infants with degenerative diseases, whose prognosis is highly predictable. The control group included infants with minor risk factors and slightly abnormal SERs in infancy and normal neurologic development after the first year, implying that the controls were chosen retrospectively. A comparison between the normative data derived from this group and norms obtained in our laboratory are quite discrepant, as the upper limits of normal in Gorke's study are abnormal values relative to our norms. Therefore subtle although significant abnormalities could not be clearly evaluated in this study.

Willis et al (1987) studied 10 asphyxiated term newborns at 2, 4 and 6 months of age with short latency SER. The authors elected not to test the children in the newborn period as the response is more difficult to interpret. All 10 had at least 1 SER and were followed to a mean age of 20

months. Neurological and developmental evaluations were performed by a pediatric neurologist and a psychologist using the Bayley Scale of Infant Development. The examiners were unaware of the SER findings. Results showed excellent correlation between SER findings and outcome in all patients. Abnormalities in the SER included absent peaks (N1/P1), or latencies > 3 standard deviations above the mean of the control group. Two or more normal SER (in 4 out of 10 patients) correlated with a normal neurologic exam whereas unilateral or bilateral absence of parietal peaks or increased latencies (in 6 out of 10) were compatible with abnormal neurologic outcome. Furthermore, examination of preliminary data revealed that persistently absent peaks were seen in children who later manifested with spastic quadriparesis, whereas absent peaks that normalized by 6 months were documented in children with mild to moderate tone abnormalities. Further studies were therefore needed to evaluate whether or not the SER can distinguish the level of disability. The SER appears to have substantial prognostic accuracy however this needed to be confirmed by a study on a larger cohort of high risk newborns.

Klimach & Cooke (1988b) performed SER testing on 30 premature infants with abnormal cranial ultrasounds at a mean conceptional age of 35 weeks Follow-up neurodevelopmental assessments were performed at the regional center (N=15), or information was derived from a questionnaire for patients transferred back to district

hospitals (N=10). Twenty-five out of 30 patients were followed between 6-16 months (median: 10 months) of age, and 3 were less than 6 months. One patient died and 1 was lost to follow-up. All with normal SERs were normal to date on follow-up. Some of these patients with normal SERs had quite abnormal ultrasounds; including bilateral or unilateral parenchymal lesions. There were 4 patients with unilateral SER abnormalities and corresponding parenchymal lesions with clinical evidence of hemiplegia. Two other patients had unilateral SER abnormalities (increased latencies); and 1 had lower extremity dystonia and the other was normal at 9 months. Nine patients had bilateral SER abnormalities, follow-up information on 7/9 revealed 6 with neurologic abnormalities and all 7 with developmental delay. The authors stipulate that the sensitivity and negative predictive power of the SER for cerebral palsy (CP) or what the authors labelled as developmental delay was 100%, with a specificity and positive predictive power for CP of 87% and 83% respectively. There were no false negatives, and few false positives when predicting CP, however there were more false positives for developmental delay. However, a bilaterally abnormal SER was 100% predictive of developmental delay. The SER on discharge (i.e. close to 40 weeks conceptional age) was more predictive than those on initial testing. The immature nervous system may "recover" from injury, thus limiting the prognostic value of positive neonatal tests. This study shows that a normal SER

correlates with a good neurodevelopmental outcome whereas abnormal SERs correlate better with motor disturbances than more global developmental delay. A bilaterally abnormal SER best predicts an abnormal outcome. This study had diverse follow-up assessment measures, that were performed at variable ages. Furthermore assessment of outcome was not performed in a blind fashion.

Willis et al (1989) recently reported on the predictive value of SERs in 39 premature, VLBW infants with periventricular hemorrhage. SERs were performed only at 2, 4 and 6 months corrected age, as neonatal test results are somewhat more difficult to interpret. Follow-up testing was carried out by a neurologist and a psychologist who were both blind to the evoked response results. Testing was performed at a mean age of 22 months, correcting for prematurity. All 15 with abnormal SERs on 1 or more occasions had abnormal Bayley Motor Scores, and 14/15 had severe abnormalities on neurologic examination. Therefore this study provides further evidence that an abnormal SER implies future neuromotor dysfunction. There was no apparent relationship between the lateralization of the hemorrhage and SER or motor abnormalities. There were false negatives in this study, however 3 normal SERs were associated with a favorable developmental outcome with a negative predictive power of 36%.

There are several methodological weaknesses in many of
the studies reported to date.   These would include:

i)an inappropriate "reference" or control group: High risk
newborns from a relatively lower risk category with only
minimal evoked response abnormalities or developmental
delays were included in the control group in studies by
Streletz et al (1984) and Gorke (1986).   As a result, cut-
off values for absolute and interwave latencies were much
higher when compared to normative data from our laboratory.

ii) inconsistent follow-up: In some studies, there was a
large age span for the age tested when determining outcome
(Gorke, 1986: 11-36 months; Klimach & Cooke, 1988: 6-16
months; Stockard et al, 1983:18 months-4 years). Different
levels and types of handicap are evident at different ages,
therefore a wide age range for measuring outcome would yield
highly variable results. Of further significance, follow-up
information was obtained by questionnaires or verbal
reports for many of the children in the study by Klimach &
Cooke (1988b), thereby increasing the variability and
decreasing the reliability of the findings.

iii) the absence of a "blind" evaluation of outcome: Except
for the studies by Willis et al (1987,1989), the existing
studies do not specify that unbiased, blind assesssments of
outcome were carried out on study patients. The neurologist
and psychologist evaluating the high risk newborns were
blind to the evoked response results in studies by Willis

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and collegues. However in no reported study are the examiners evaluating both healthy and high risk newborns in a blind fashion.

iv) evaluation of a high risk population with a predictable outcome: Two studies (Gorke, 1986; Stockard et al, 1983) have included patients with genetic syndromes or degenerative diseases where evoked responses and ultimate outcome are likely to be abnormal. The predictive value of evoked response testing may be magnified by the inclusion of those children with a predictable prognosis.

v) the absence of evoked response testing in the newborn period (approximately 40 weeks conceptional age): False negatives appear to be a significant problem in studies where testing was carried out in infancy only (Gorke, 1986; Hecox & Cone, 1981; Willis et al, 1987; Willis et al, 1989). It is possible that many subjects with normal evoked responses in infancy would have had abnormal responses initially, and subsequent morbidity.

vi) poorly defined recording techniques (Hrbek et al, 1977) or the use of non-standard stimulating and recording parameters (Klimach & Cooke,1988b): This decreases the feasibility of other laboratories applying the reported findings for clinical purposes.

In spite of these methodological problems in the studies reported in the literature, the SER appears to be an

effective predictor of neuromotor sequelae in high risk neonates.

In the 4th article: "The prognostic significance of multi-modality evoked response testing in high risk newborns", 44 high risk newborns and 14 healthy neonates were tested with multi-modality evoked responses in the newborn period. Serial testing was carried out at 2 and 6 months corrected age. At 1 year of age, all patients and controls were evaluated in a blind fashion by a pediatric neurologist and clinical psychologist. The results of this prospective study indicate that an abnormal SER or ABR correlated with neurologic impairment at 1 year of age. Furthermore, the degree of SER abnormality (i.e. persistent versus an improving picture on serial testing) reflected the extent of neurologic sequelae. Normal multi-modality evoked responses (ABR and SER) predict normal developmental scores in all areas. Finally, ABR and SER waveforms that are both identifiable and of normal latency have a strong positive and negative pred·_tive power for neurologic status at 1 year of age.

This study clearly demonstrates that multi-modality evoked responses are excellent predictors of neuromotor outcome in high risk newborns. This study further emphasizes the importance of testing patients in the newborn period to diminish possible false negative findings. Serial testing in infancy is of great value in delineating the degree of subsequent neuromotor handicap.

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Study Rationale

Prenatal or perinatal brain injury or maldevelopment seen in asphyxiated, small for gestational age or very premature infants continues to be of paramount concern to clinicians, despite improvements in obstetrical care, resuscitation procedures and neonatal intensive care Although prevention is the primary goal, early identification of those who have suffered an insult to the maturing brain is important, so that effective remediation may be initiated expediently (Amiel-Tison & Ellison, 1986).

Animal models of anoxic-ischemic brain damage as well as neuropathologic, clinical and neuroradiologic observations indicate that a wide spectrum of brain damage can occur (Hill & Volpe, 1981; Myers, 1975; Volpe, 1987) These patterns of injury vary in degree and extent, and are related to the nature of the insult and the level of maturation of the brain. Volpe has clustered these patterns into 5 major identifiable neuropathologic varieties selective neuronal necrosis, status marmoratus, parasagittal cerebral injury, periventricular leucomalacia and focal/multifocal ischemic brain necrosis. These patterns are unique with respect to the nature of the insult, the topography of the lesion, and the evolution and pathogenesis of the injury (Volpe, 1987).

Presently, there are no clinical or laboratory assessments that accurately evaluate the type or severity of brain injury, or precisely determine the prognosis,

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particularly when mild to moderate deficits exist (Majnemer et al, 1988; Volpe, 1987). Evoked response is a non-invasive, objective electrophysiologic test that be of value in identifying the extent of damage to the maturing nervous system (Chiappa, 1983). In a previous study at the Evoked Potentials Laboratory at the Montreal Children's Hospital (Majnemer et al, 1988; Majnemer, MSc thesis, 1985), the prognostic significance of the ABR was examined in high risk newborns. ABR testing was carried out in the newborn period and repeated again in infancy. Neurodevelopmental outcome at 1 year corrected age was measured by 2 blind evaluators, a neurologist and a psychologist. The results of this study showed that increased brainstem conduction time predicted gross motor delay as well as neurologic impairment with a strong positive predictive power and specificity. False negatives were a problem however, as a normal ABR did not ensure a normal outcome. It is conceivable that the ABR was sensitive to one pattern of injury, such as selective neuronal necrosis following anoxia, which involves selective damage to the auditory relay nuclei as well as other important cortical and subcortical structures (Myers, 1975). However other patterns of injury exist, that may not significantly involve the brainstem structures. In particular, the ABR was a poor predictor of outcome in premature infants. This is likely due to the fact that a common pattern of injury in very premature infants would involve the subependymal germinal

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matrix or intraventricular/periventricular region. The
particular vulnerability of this region may be attributed
to the fragile vascular bed and concommitant large portion
of cerebral circulation perfusing the ventricular region.
An initial bleed as a result of cerebral blood flow changes
(due to hypoxia, hypercapnea, or acidosis) may rupture into
the adjacent ependymal layer. Ischemic necrosis of
periventricular tissue due to impaired circulation (i.e
hypotension during apnea) may cause further destruction of
the adjacent white matter (Volpe, 1989). The ABR evaluates
the integrity of brainstem structures only, therefore
evidence of periventricular leucomalacia would not be
elucidated by ABR testing.

Therefore a second prospective study was initiated,
with the aim of evaluating a wider distribution of the
ascending neuraxis using multi-modality evoked responses.
Using both ABR and SER, caudal and rostral structures could
be evaluated simultaneously. The results of this second
study demonstrate that the SER in particular correlates
strongly with the degree of neuromotor handicap at 1 year of
age. Furthermore, a normal ABR and SER are compatible with
a favorable neurodevelopmental outcome. Abnormalities in
the SER were more prevalent and this may be partially due to
the fact that the SER evaluates a greater extent of the
nervous system; notably thalamo-cortical and cortical
projections. These higher centers are particularly
vulnerable to injury in high risk newborns. Secondly, very

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abnormal ABRs(i.e. absent peaks) are often not compatible with life, however absent peaks in the SER are compatible with survival but with significant morbidity (Frank et al, 1985). This study has shown that a sensory evaluation can be used to predict neuromotor deficits at 1 year corrected age. This is probably due to the close proximity of the sensory and motor pathways and cortical structures. Presumably the superimposed sensory deficit would further compromise motor function due to the deficiency in sensory feedback.

Original contributions of this study

Important original contributions of this study include:

i) the establishment of normative data for SER in newborns and infants: Normative data for the ABR has been described by several laboratories in the literature (Jacobson et al, 1982; Krumholz et al, 1985; Starr et al, 1977), however few laboratories have attempted to perform SERs in young infants for research or clinical purposes. Therefore to begin with in this study, appropriate stimulating and recording parameters as well as testing procedures were delineated to minimize artifact and maximize the reproducibility and reliability of the SER recordings. Longitudinal testing of the same healthy newborns was carried out on 3 or 4 occasions over the first 7 months of life. Maturational changes in waveform identifiability, absolute and interwave

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latency, degree of dispersal and relative amplitude of waveforms were statistically analyzed and described. The changes that accompanied altering sleep states, and the effects of 2 commonly used filter settings on the SER were summarized as well.

ii) the examination of the effects of gestational age at birth on the SER: The literature has demonstrated that ABR latencies decrease as a function of conceptional age (defined as gestational age plus postnatal age), not chronological age. Therefore, these studies support the view that myelination continues at a fixed rate irrespective of intrauterine versus early extrauterine exposure. This principle has been assumed for SER latencies but has not been validated. As part of this prospective study, SER findings in low risk, healthy premature infants tested at term were compared to those of healthy full term newborns. Infants were matched for conceptional age. Both absolute and interwave latencies as well as waveform morphology were indistinguishable in infants of the same conceptional age.

iii) serial evoked response evaluation of both healthy and high risk newborns, beginning in the newborn period In no other reported longitudinal study using evoked potentials, is a reference group being evaluated simultaneously with the study group. In this manner, normative data is derived from a group being evaluated using the identical testing procedures and examiners as the high risk group.

Furthermore, evaluators of developmental outcome are blind to the evoked response results as well as to the medical history (i.e. healthy versus high risk) of each child.

Testing in the newborn period appears to be critical in decreasing the number of false negative findings. Testing in the NICU while the high risk newborn is medically unstable is not advisable due to the technical difficulties encountered with this environment. However testing the neonate when medically stable, closer to discharge, appears to increase the prognostic value of this test (Hakamada et al, 1981; Stockard et al, 1983). Serial evaluation in infancy is crucial as the evolution of any abnormalities can be examined carefully. This study has demonstrated that this is invaluable in differentiating the severity of subsequent disability. Interpreting a single evoked response test would inevitably decrease the prognostic power of this test.

iv) the use of multi-modality evoked responses: A wider distribution of the nervous system may be objectively evaluated using multi-modality evoked responses. Important caudal and rostral structures are examined simultaneously using both ABR and SER.

v) A comparison between a standardized, neonatal neurologic assessment (Einstein=ENNAS) and multi-modality evoked response testing was made. Chi square analysis revealed no significant relationship between the ENNAS deviant score and

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neonatal evoked response findings. Furthermore, in contrast to evoked response testing, the ENNAS was a poor predictor of neurologic outcome. A normal ENNAS was associated with normal developmental scores in most children. There have been very few studies that have compared evoked response findings with neurobehavioral assessments in high risk newborns. In one study, the I-V interval of the ABR had low but reliable correlations with 4/11 variables in the Brazelton Scale (Murray, 1988). In a second study by Eldredge & Salamy (1988), abnormalities in the Neurological and Adaptive Capacity Score (NACS)were relatively common in 15 high risk newborns whereas only 1/15 had an abnormal ABR. The authors conclude that the NACS is sensitive to mild but diffuse disturbances whereas the ABR reflects anoxic insult to brainstem structures. Specific items or clusters of items on the ENNAS together with the ABR and SER may have a greater predictive value, however further research in this area is needed.

Relevance

Researchers and clinicians agree that it is difficult to accurately predict neurodevelopmental outcome in high risk newborns before the first year, although extremes of outcome can be predicted with reasonable assurance. For example, isoelectric or burst supression EEGs, significant structural lesions on CT such as a porencephalic cyst, or extensive hypodense areas on ultrasound are linked with

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severe neurologic dysfunction. However, mild to moderate developmental deficits are not easily predicted. Furthermore, transient versus permanent developmental disturbances cannot be readily differentiated (Amiel-Tison & Ellison, 1986; Illingsworth, 1987). Therefore more effective prognostic tests for graduates of the NICU are needed. Accurate prediction offers the family a more realistic view of their child's prognosis. Those identified or "diagnosed" early to be at high risk for developmental problems would be followed closely and treated optimally. Formal therapeutic intervention programs may begin early, so as to reduce the secondary effects of neurologic handicap, as well as to maximize the functional potential of the child (Rosetti, 1986). The ability of therapeutic interventions to enhance or improve outcome has not been adequately proven in the literature. Therefore the efficacy of treatment programs or a comparison between 2 therapeutic approaches may be more effectively evaluated if study patients are first grouped by relative risk for handicap A specific early intervention program may prove to be more successful for infants at risk for only mild to moderate developmental deficits, however this finding may be masked by including infants from all possible outcome categories.

The results of this prospective study, which examines the prognostic value of multi-modality evoked responses in high risk newborns, has demonstrated that the ABR and SER

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are accurate predictors of neuromotor outcome at 1 year corrected age. Serial testing in infancy is of particular value for the SER as the evolution of the response reflects the extent of neurologic handicap Multi-modality testing in the newborn period has yielded a high sensitivity and specificity for neurologic handicap at 1 year of age The low false positives are particularly significant, as few patients were falsely labelled. A normal ABR and SER were associated with normal developmental scores in all areas of development.

This study clearly illustrates that multi-modality evoked response testing is a useful adjunct to the clinical examination and neuroradiologic investigation of the high risk newborn, thus improving the clinician's perspective of a child's prognosis (see appendix A for example of 2 cases).

Evoked response testing cannot stand alone as a predictive test, however this study has clearly demonstrated that it is an _important_ part of the neurologic investigation of the high risk newborn. A combination of assessment measures, such as EEG, evoked response, cerebral imaging and the neurologic exam would likely yield more precise prediction of outcome. This study emphasizes the importance of newborn testing followed by serial testing in infancy, so that the presence and extent of neurologic disability may be more accurately predicted.

APPENDIX A: 2 case histories that demonstrate the importance of evoked response testing in providing valuable prognostic information to the clinician.

Baby KF·

This infant suffered severe birth asphyxia requiring resuscitation and cardiac massage. The initial EEG showed a burst suppression pattern however subsequent recordings improved and normalized, and the child's clinical presentation improved rapidly as well. CT showed only minimal anoxic changes. The SER demonstrated absent N19 peaks bilaterally and this abnormality persisted to 6 months of age. In the ABR, there was an increase in I-III interwave latency This child, now three years of age, has severe spastic quadriparesis and limited motor development.

Baby JE

This neonate had severe perinatal asphyxia with meconium aspiration and a pH of 6.65. EEG showed a burst suppression pattern and epileptiform activity. Follow-up recordings over the first months of life remained abnormal with sharp activity and some depression. CT demonstrated hypoxic changes and the child was very hypotonic and lethargic on discharge. This infant had a normal ABR and SER and subsequently had normal developmental scores and a normal neurologic examination at 1 year of age.

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