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NEUROBEHAVIORAL STATUS OF NEWBORNS WITH CONGENITAL HEART DEFECTS

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STATEMENT OF AUTHORSHIP:

I certify that I am the primary author of the manuscript contained in this thesis. I claim full responsibility for content and style of the text included herein.

ABSTRACT

Controversy exists regarding the integrity of the nervous system in the young infant with a congenital heart defect who must undergo corrective or palliative open heart surgery. Neurodevelopmental sequelae have been largely attributed to surgical events and procedures without careful evaluation of preoperative neurologic status. Very few studies have explored whether pre-existing neurologic abnormalities are evident prior to surgery.

The objective of this study was to determine if newborns with congenital heart defects demonstrate abnormalities in neurobehavioral status prior to surgery, as measured by neurologic and neurobehavioral performance as well as somatosensory evoked potentials. The results indicated that neurobehavioral abnormalities were common and included muscle tone abnormalities, seizures, microcephaly, poor state regulation, poor orienting responses, and abnormal feeding patterns. The overall likelihood of neurobehavioral abnormalities was not influenced by clinical indicators of cardiorespiratory compromise. Findings suggest that the prevalence of neurobehavioral abnormalities in this population has been underappreciated and may warrant routine developmental screening.

SOMMAIRE

Il existe une controverse eu ce qui concerne l'intégrité du système nerveux centrale chez le jeune enfant avec une cardiopathie congénitale, qui doit subir une chirirgie à coeur ouvert palliative ou de rectification. Les séquelles neurodeveloppementales ont été grandement attribuées aux procédures chirurgicales sans une évaluation attentive and soigneuse du status neurologique préopératoire. Très peu de recherches ont evalué la possibilité que des anomalies neurologiques avant la chirurgie puissent exister.

L'objectif de cette étude est de déterminée si les nouveaux nés avec une cardiopathie congénitale démontrent des anomalies dans leurs status neurobehaviorale avant la chirurgie en mesurant leurs performances neurologiques et neurobehaviorales ainsi que des potentiels evoqués somatosensoriels. Les anomalies neurobehaviorales étaient fréquentes et comprenaient des anomalies au niveau du tonus musculaire, convulsions, microcèphalie, un état de régulation pauvre, des réponses d'orientation pauvre, et des patrons d'alimentation anormaux. Dans l'ensemble, il est peu vraisemblable que les anomalies neurobehaviorales augmentent pat la gravité de l 'état cardio-respiratoire.

Les résultats de nos recherches nous suggèrent qu'il y a eu sous-estimations de la prédominance des anomalies neurobehaviorales chez cette population et justifieraient alors la nécessité d'un dépistage du développement régulièrement.

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PREFACE

The recent successful application of open heart surgery in young infants with congenital heart defects, along with an increasing trend to very early surgical intervention of the most severe cardiac malformations necessitates a formal reevaluation of the central nervous system in infants with congenital heart defects (Ferry, 1987; Stuart et al., 1994). Considerable controversy exists in the literature regarding the presence and likelihood of neurologic sequelae in children undergoing open heart surgery. To date, neurologic abnormalities have been primarily related to surgical related stresses without careful baseline evaluation of neurologic status (Ferry, 1987, 1990).

Long-term follow-up studies indicate that these children commonly demonstrate behavioral, language and learning difficulties at school age (Bellinger et al., 1991; Haka-Ikse et al., 1978; Mendoza et al., 1991). It has become essential to determine if pre-existing neurologic dysfunction is present in this population prior to surgery, and if this in turn may increase the probability of surgical complications and neurodevelopmental outcome. Very few studies have ascertained preoperative neurodevelopmental status, therefore the incidence of preexisting neurolgic and/or developmental problems in this population is unknown.

In chapter one, the literature on infants with congenital heart defects and neurologic sequelae will be reviewed, as well as electrophysiologic and

radiological evidence. Chapter two summarizes the methodology used to identify and recruit subjects. The selection criteria for subjects, and evaluation procedures are delineated. Results of the study are presented in chapter four. The final chapter summarizes the findings of this study. The significance of the study and the relevance to clinical practice are also described.

In summary, this study examines the neurobehavioral status of newborns with congenital heart defects prior to open heart surgery. Neurologic, neurobehavioral and electrophysiologic findings are described. The relative contribution of cardiac related stresses on the immature nervous system and the relationship between cardiorespiratory compromise and neurobehavioral findings is explored. The factors affecting the neurodevelopmental outcome of children with congenital heart defects are undoubtedly complex, and are likely to involve the interaction of preoperative, intraoperative and postoperative factors. Early identification of 'at-risk' newborns is critical in order for health care delivery to be most effective in the prevention and/or early remediation of developmental deficits.

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1. LITERATURE REVIEW

1.1 Congenital heart defects (CHD)

A CHD is defined as a gross structural abnormality of the heart or of the major thoracic vessels that is of functional significance (Nuutinen et al., 1989). The incidence of congenital heart disease is 8 per 1000 livebirths and the incidence of children with CHD that will require medical and surgical interventions is 3.5/1000 live births (Ferry, 1990). CHD occur as isolated defects in slightly more than 50% of cases, while in the remaining cases it occurs in conjunction with a malformation, chromosomal defect, or syndrome. These defects may be classified as cyanotic which involve mixing of oxygenated and deoxygenated blood in systemic circulation, resulting in cyanosis (e.g. tetralogy of fallot, transposition of the great vessels, pulmonary or tricuspid atresia), acyanotic where there is anatomic communication between the chambers of the heart, resulting in a left-to-right shunting of blood (e.g. atrial or ventricular septal defects, patent ductus arteriosis) and obstructive, which consists of an interruption and obstruction of appropriate blood flow within the heart or vessels connected to the heart (e.g. coarctation of the aorta, pulmonary or aortic stenosis) (Park, 1984). Recent improvements in diagnostic testing and surgical techniques have enabled correction or palliation of most complex CHD during early childhood, resulting in dramatic reduction in mortality and morbidity in these children (Clare, 1985; Ferry, 1987; Stuart et al., 1994).

1.2 Surgical intervention

Surgical intervention early in life is often necessary in infants with CHD

because of persistent cardiac failure or arterial hypoxemia (Brunberg et al., 1974; Ferry, 1990). Cardiopulmonary bypass (CPB) is a technique by which the systemic circulation is maintained while the heart is arrested during surgery. This technique involves the drainage of anticoagulated blood by gravity from the right heart and caval veins into an oxygenator, where gas exchange takes place. Oxygenated blood is then pumped back into the ascending aorta with sufficient pressure to disperse the blood into the systemic circulation. An aortic cross-clamp is used to occlude the coronary circulation and prevent perfusion of the myocardium, thus allowing the surgeon to operate with the heart stopped, in a blood-free surgical field. During CPB, the patient's core temperature is reduced to 22°-26°C, in order for systemic oxygen requirements to be decreased (Stuart et al., 1994). Although CPB has been proven helpful in the adult population and in older children, this intraoperative extracorporeal perfusion technique is less well tolerated in young infants (Ferry, 1987).

The technique of deep hypothermia coupled with circulatory arrest (DHCA) was introduced in 1963 by Horiuchi et al. as an alternative to standard CPB for repairing cardiac anomalies. This technique was further developed by Mohri's group (Stevenson et al., 1974) and consists of cooling the patient's core temperature to 15°-18°C and arresting the circulation completely. A major benefit of this procedure is that it minimizes the duration of CPB and it allows for rapid, accurate repair in a bloodless, motionless operative field unencumbered by venous cannulae, which is especially valuable in the repair of the very small heart (Brunberg et al., 1974; Newburger et al., 1993). Cooling reduces the systemic oxygen requirements, assumably to maintain cell viability (Stuart et al., 1994). The use of circulatory arrest is based on the premise that there is a "safe" duration

that is inversely related to body temperature; the organ with the shortest safe circulatory arrest time is the brain (Newburger et al., 1993).

Alternatively, low flow CPB maintains continuous cerebral circulation during surgery and has been advocated as preferable with regards to neurologic outcome. However the use of low flow CPB prolongs the time required for extracorporeal circulation, which in turn is known to increase pump-related sources of brain injury. In many cases, the surgeon is unable to successfully repair complex defects without a period of DHCA (Brunberg et al., 1974).

Considerable controversy exists with respect to neurologic morbidity and the relative contribution of CPB versus DHCA on central nervous system damage following open heart surgery (Ferry, 1987; Mayer, 1991; Newburger et al., 1993). Presumably, a longer duration of circulatory arrest time (>45-60 minutes) and an increased depth of cooling appear to be associated with a greater likelihood of brain injury. Furthermore, the reported incidence of neurological complications resulting from open heart surgery varies widely depending on the type of study, and is estimated to range from 7% to 61% for transient complications and from 11.6% to 23% for permanent deficits. To date, careful prospective neurologic and developmental evaluations prior to and following surgery have rarely been performed in this population, therefore the exact nature and extent of neurdevelopmental sequelae is unknown (Bellinger et al., 1995; Ferry, 1990; Newburger et al., 1993).

1.3 Preoperative neurological dysfunction in infants with CHD

The integrity of the developing nervous system emerges as a complex interaction between preoperative, intraoperative and postoperative factors in children with CHD. According to Volpe et al. (1993), certain congenital cardiac

lesions are associated with an appreciable incidence of accompanying cerebral maldevelopment and all cardiac lesions are associated with an increased risk of perinatal and presurgical hypoxic-ischemic brain injury. Other perinatal factors that predispose infants with CHD to neurologic deficits include neonates that are small for gestational age or low birth weight, reduced head circumference or low socioeconomic status (Fishman & Parke, 1993). Recent dramatic reduction in surgical mortality following repair of congenital cardiac lesions has been accompanied by a recognition that survivors frequently suffer neurologic sequelae (Ferry, 1990).

Although there is considerable concern regarding the likelihood of adverse neurological sequelae following cardiac surgery, the exact incidence, nature, and severity of neurologic sequelae are uncertain, particularly when considering the preoperative versus the postoperative neurologic status of these patients. In many infants with CHD, preoperative neurological dysfunction may not be recognized because of the early age at which surgery is performed, the general 'illness' of the infant as a result of the cardiac defect, and the lack of objective neurological assessment (Stuart, 1994).

1.3.1 Risk of hypoxic-ischemic brain injury: Brain injury is often related to complications of open heart surgery (OHS) however neurologic outcome may also be influenced by pre-existing brain abnormalities as a result of cardiac-related effects including, severe chronic hypoxemia, congestive heart failure, episodes of arrhythmia, cardiac arrest, metabolic encephalopathies, ischemias or thromboembolic events unrelated to surgery (Newburger, 1992). In a retrospective study by Puntis et al. (1989), the authors describe neurologic outcome in 37 children (3 days - 10 year age range) following OHS. Although the

exact number of subjects who underwent cardiovascular surgery was not determined, it was estimated to be approximately 2500 cases over a 10 year period. Chart reviews revealed that 37 children were identified to have overt neurologic dysfunction. In two-thirds of these subjects, neurologic sequelae were felt to have occurred in association with cardiovascular surgery (i.e. deficits evident in the immediate postoperative period), while in one-third neurologic complications were attributed to their underlying cardiovascular disease and unrelated to surgery. Although these children were considered neurologically normal prior to surgery, no formal evaluation was carried out. Pre-existing neurologic abnormalities may thus be incorrectly attributed to complications resulting from cardiovascular surgery. Additionally, pre-existing brain lesions or conditions may be exacerbated by sustaining additional insults during the operative procedure.

Children with CHD may also present with an increased susceptibility for neurologic complications including seizures, cerebrovascular accidents, cerebral arterial or venous thrombosis, cerebral abscess, and other complications that may result in neurologic sequelae. These neurologic complications may occur in as many as 25% of these children, and are at times life-threatening (O'Dougherty et al., 1983). Children with CHD can thus experience multiple medically and surgically related stresses, which may heighten the possibility of later dysfunction.

Children with cyanotic (defined as dark blue/purple coloration of the skin due to deficient oxygenation of the blood) CHD are reported to be at greater risk of neurologic complications (Stuart, 1994). According to Aram et al. (1985), chronic cyanosis is associated with a small though significant reduction in intelligence score compared to 'normals', independent of the degree of illness, age, socioeconomic status, neurological or genetic status, or surgical intervention.

Other investigators have found an increased prevalence of acquired neurological dysfunction in children with unoperated congenital heart disease, including neuronal deafness, motoric and intellectual deficits as well as behavioral disturbances, that seems to be reflective of a chronically disturbed cardiovascular physiology and its effects on brain development (Stuart, 1994).

Children who require cardiac transplantation or those with hypoplastic left heart syndrome are reported to be particularly at risk for developing preoperative and postoperative neurological abnormalities given their complex cardiac physiology (Glauser et al., 1990; Stuart, 1994). Preoperative neurological dysfunction may also be the consequence of emboli following diagnostic procedures or treatments such as cardiac catheterization, balloon atrial septostomy or balloon valve angioplasty (Stuart, 1994).

A number of complications of perinatal asphyxia have been described in newborns with CHD. These include hypoxic-ischemic encephalopathy, nephropathy, persistent pulmonary hypertension, hyperammonemia, and a syndrome of inappropriate antidiuretic hormone secretion. Closer attention must therefore be paid not only to cardiac signs, but to neurologic manifestations as well as renal and metabolic functions in these patients during the first few days of life in order to ensure that the central nervous system (CNS) has not been compromised (Newburger, 1992).

1.3.2 Risk of congenital brain malformation: There is some suggestion that congenital malformations of the CNS may co-exist in a subset of individuals with CHD (Newburger, 1992). Miller et al. (1993) performed magnetic resonance imaging (MRI) on 23 children with CHD following open heart surgery, at a mean age of 66 months. Abnormal scans were found in 74% and most commonly

included, diffuse hypoxic-ischemic encephalopathy and focal cortical infarction. In addition, callosal agenesis and abnormal neuronal migration was discovered in 1 patient. In this study, of 104 children who underwent open heart surgery, 27 died and 20 refused to take part in follow-up testing. Of the 57 subjects that underwent psychological testing, 23 agreed to have MRI testing. Given the apparent selection bias, generalizability of the findings is limited. Bellinger and colleagues (1995) also performed MRI testing on 142 subjects at 1 year of age following open heart surgery, and found that 3 children exhibited malformations including left temporal lobar hypoplasia, Chiari type I malformation or a small arachnoid cyst in the left sylvian fissure. Burn (1987) lists 32 syndromes where a CHD is associated with congenital neurologic lesions and subsequent mental retardation. For example, 5% of children with CHD have Down syndrome.

1.3.3 Neonatal neurologic status: Although many risk factors for acquired neurologic injury early in life have been suggested, a review of the literature reveals that only one study has actually described the neonatal neurobehavioral status of infants with CHD. Gillon (1973) summarized her observations of 82 newborns with cardiac distress prior to surgery (24 hours to 8 weeks of age), over a two year period in the context of ongoing nursing care. Respiratory difficulties such as abnormal breathing (n=72), tachypnea (n=14), and respiratory distress (n=55) were documented. Feeding difficulties, including poor coordination of sucking, swallowing and breathing were noted in 63 newborns. Many exhibited emesis, poor suck and decreased efficiency while feeding. Activity level was also observed, with restlessness (n=15), lethargy (n=22), and poor attentiveness to stimuli (n=26) commonly reported. The majority of the babies were found to be

cyanotic (n=57), with the cyanosis reportedly fluctuating with position, and worsening particularly in supine. Decreased muscle tone was documented in 15 babies while posturing and hypertonia was described in 4 cases. According to the author, these abnormal behaviors were not merely reflective of cardiac malfunction, as one would expect that the newborn's neurobehavioral response to illness would be a generalized one (e.g. lethargy, low tone and poor associated with cardiac illness, this was not substantiated by any empirical data. Limitations of this study include a lack of formal neurobehavioral and neurologic assessment as well as no formal statistical applications. Furthermore, the behaviors documented were largely reflective of subjects cardiorespiratory status (e.g. color, heart rate, activity level, feeding, etc.) with little emphasis on neurobehavioral performance.

1.3.4 Preoperative neurologic status: Few studies to date have formally evaluated children with CHD prior to OHS. Clarkson et al. (1980) reported that 10 of 12 subjects had abnormal neurologic status prior to surgery. In this study, subjects with neurologic deficits such as perinatal asphyxia, seizures, hypotonia or motor delay that could be attributed to their cardiac disease were excluded. Blackwood and coworkers (1986) performed formal pre and postoperative neurologic assessments on 36 subjects. Examinations were carried out by a pediatrician in a blind fashion and results showed that preoperatively, 5 children had microcephaly, 4 were hemiparetic and 1 was hypotonic. Similarly, Brunberg et al. (1974) assessed neurologic status in 21 of 22 subjects (4 days to 24 months of age) preoperatively and found that only 6 had normal exams. Psychomotor delay was present in 62%, hypotonia in 43% and seizures, motor asymmetry, and

general central nervous system dysfunction was reported in 1 patient. Electroencephalographic abnormalities were documented in 5 out of 15 tested.

Although it has been suggested that children that present with neurologic abnormalities prior to surgery may be more susceptible to further neurologic injury, empirical data is lacking (Ferry, 1987; Huntley et al., 1993; Stevenson et al., 1974).

1.4 Short-term neurologic sequelae following open heart surgery

Although the precise prevalence of neurologic sequelae is unknown, neurologic complications following open heart surgery continue to be reported in both the adult and pediatric literature (Ferry, 1987; Gilman, 1990). To date, various signs and symptoms have been described, that may be transient or persistent in nature. Neurological complications reported in the immediate postoperative period following open heart surgery in adults include seizures, states of altered consciousness, personality changes, stroke, abnormal muscle tone, incoordination, tremor, paresis, spinal cord lesions, gaze palsies and other cranial nerve abnormalities, as well as dyskinetic movement patterns. In children, a range of neurologic sequelae is possible, however the literature has recently focused on case reports describing a movement disorder manifested by choreoathetosis.

Certain studies have examined the developmental outcome in children with CHD following surgery reported that the use of profound hypothermia with circulatory arrest resulted in adverse affects on psychomotor development. Brunberg et al. (1974) found definite though often subtle neurologic abnormalities may have been related to a period of circulatory arrest in spite of, or perhaps due to, deep hypothermia. Furthermore, Veelken et al. (1992) also investigated the incidence of neurologic complications following anatomical correction of

transposition of the great arteries in a consecutive series of 38 children (10 day - 23 month age range). Psychomotor performance was assessed using the Griffith Developmental Scales for younger children and the Denver Developmental Screening Test for older ones, as well as clinical neurological examinations. EEG recordings and computed tomography scans were also carried out. The authors described various neurologic sequelae in 44% of subjects including, cerebrovascular abnormalities resulting in varying degrees of spastic hemiparesis, focal epilepsy, and psychomotor retardation. However, the time of postoperative assessment as well as the functional impact of these neuromotor findings on motor development has not been described. Moreover, baseline neurodevelopmental status was not established.

Recently a randomized single center clinical trial was initiated by Newburger and colleagues (1993) to compare the incidence of brain injury in 171 infants under 3 months of age with transposition of the great arteries with either an intact ventricular septum or a ventricular septal defect undergoing an arterial switch operation after assignment to a strategy consisting predominantly of DHCA with that of children assigned to a strategy consisting predominantly of low flow CPB. In the early postoperative period, the infants assigned to DHCA presented with a higher incidence of neurologic morbidity than those assigned to CPB. In the same cohort, developmental and neurologic follow up assessments were carried out at one year of age in 155 subjects (Bellinger et al., 1995). The infants assigned to DHCA had a lower mean score on the Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development , and a higher proportion had scores <80 (i.e. 2 SD or more below the population mean). The score of the PDI was found to be inversely related to the duration of circulatory arrest ($p=0.02$). The risk of neurologic abnormalities increased with the duration of circulatory

arrest (p=0.04). The method of support however was not associated with the prevalence of abnormalities on MRI scans of the brain, scores on the Mental Development Index on the Bayley Scales, or scores on a test of visual-recognition memory. Perioperative EEG seizure activity was associated with lower scores on the PDI (p=0.002) and an increased likelihood of abnormalities on MRI (p<0.001). It is important to note that although preoperative neurologic testing was carried out, with possible neurologic abnormalities reported in 20% of subjects and definite neurologic abnormalities in 40%, these results were not correlated to early postoperative status or neurodevelopmental outcome at 1 year of age. Furthermore preoperative evaluations were limited to an examination by a neurologist and did not include standardized developmental assessment.

There have been at least 50 cases described in the literature of children with a movement disorder apparent in the acute postoperative period, typically beginning between 2-8 days (median 4-5 days) following OHS (Brunberg et al., 1987; Curless et al., 1994; Deleon et al., 1990; Huntley et al., 1993; Robinson et al., 1988; Straussberg et al., 1993; Wical & Tomasi, 1990; Wong et al., 1992). An initial latent period has been found to precede the manifestation of clinical symptoms, and the movement disorder can therefore be distinguished from a wide spectrum of withdrawal symptoms that have been documented following the delivery of opiate anesthesia (e.g. fentanyl) by continuous infusion (Lane, 1992). This movement disorder is estimated to occur in less than 1% to 25% of cases, depending on the characteristics of the cohort being studied (Curless et al., 1994; Ferry, 1990; Huntley et al., 1993; Wong et al., 1992). A variety of symptoms have been described including, choreoathetosis and oral-facial dyskinesia, hypotonia, affective changes such as irritability and pseudobulbar signs (Wical & Tomasi, 1990). The disorder has been described as varying in severity from mild to

severe. Two groups of investigators have reported that mild choreoathetosis has been more frequently described in younger children (median 4.3 months), is more transient in nature and was associated with a favorable outcome, whereas severe choreoathetosis was observed more commonly in older, cyanotic children (median 16.8 months), and associated with a poor neurologic outcome (Wical & Tomasi, 1990; Wong et al., 1992). Overall, children with this movement disorder have improved over weeks or months, however residual neurologic deficits were often documented. This movement disorder occurred following total circulatory arrest or CPB, although all children had deep and prolonged hypothermia (Huntley et al., 1990). According to Bjork and Hultquist (1962), rapid induction of hypothermia and rapid rewarming also correlated significantly with the appearance of this movement disorder. The long-term significance of these abnormal movement patterns on neurodevelopmental outcome and/or morbidity has not been ascertained.

It should be noted that in a survey of six major pediatric cardiac surgery units, neurologists indicated that they were primarily consulted to assess severe movement disorders or seizures in this patient population. These were estimated to occur in 8% (median) of children after cardiac surgery. They indicated that this estimate of acute neurologic morbidity was probably falsely low. It is likely that subtle neurologic deficits are underappreciated at present (Hesz et al., 1988).

1.5 Long-term follow-up of children with CHD

Several studies have examined the long-term neurodevelopmental outcome of children with CHD following OHS. Long term developmental sequelae following open heart surgery include neurologic abnormalities such as cerebral palsy or seizure disorders, intellectual deficits such as mental retardation, learning

disabilities and behavioral problems. The exact incidence of these sequelae is difficult to estimate due to methodological shortcomings encountered in these studies (Ferry, 1987). Unfortunately, few prospective studies exist, and many studies have used small sample sizes, non-standardized assessments, and lack systematic and comprehensive follow-up evaluations of their cohorts. The age range of the subjects at their follow-up assessment has been well over 3 years in most studies (32-90 month age ranges (Blackwood et al., 1986; Henz et al., 1988; Mendoza et al., 1991; Messmer et al., 1976; Haka-Ikse et al., 1978), rendering interpretation of results difficult. Clarkson et al (1980) examined 72 children (mean age 47.9 months, range 29-84 months); however, most other studies have used sample sizes below 40 (and less than 20 in 2). In most studies, preoperative neurodevelopmental status was unknown, or available only in a small subset of subjects assessed over a long-term period (Ferry, 1990). As a result, any conclusions drawn regarding possible correlations between surgical events and outcome should be interpreted with caution.

Overall, the long-term outcome of children with CHD following surgical repair of CHD has been controversial. Some studies have reported favorable neurodevelopmental outcomes, while others have documented developmental lags (Ferry, 1987). Clarkson et al. (1980) found no difference in mean IQ scores in 72 subjects (24-84 month age range) with CHD as compared to age-matched controls. Bender et al. (1979) concluded that the used of circulatory arrest during profound hypothermia had no long-term deleterious effects on the developmental outcome in a group of 128 subjects, however no formal testing was applied. When reported, deficits include intellectual dysfunction, language delays (Bellinger et al., 1991; Haka-Ikse et al., 1978; Hesz et al., 1988; Messmer et al., 1976; Wells et al., 1983), as well as social and educational problems (Nuutinen et

al., 1983; O'Dougherty et al., 1983). Neurologic abnormalities reported have ranged in prevalence between 17-78% of subjects (Brunberg et al., 1974; Mendoza et al., 1991, O'Dougherty et al., 1983). O'Dougherty and colleagues (1983) evaluated 34 children with CHD at a mean age of 9.1 years, and found that only 23% of subjects had normal neurologic examinations. Furthermore, 42% required special classroom placement or individualized instruction for learning and/or behavioral difficulties. Motor skills have only been formally assessed in two studies, and gross motor delay and motor incoordination were commonly reported in both (Blackwood et al., 1986; Haka-Ikse et al., 1978).

1.6 Electrophysiologic techniques as indicators of brain injury

1.6.1 Evoked potentials: Evoked potentials objectively and noninvasively assess the functional integrity of ascending neuronal pathways (Chiappa, 1990). Evoked potential recordings from animals following periods of hypoxia or ischemia demonstrate that the auditory brainstem and somatosensory evoked potentials are altered significantly in amplitude and latency by these events. The nature of these abnormalities appear to relate to the evolution of the resulting lesion. (Branston et al., 1984; Coyer et al., 1986; McPherson et al., 1986). These electrophysiologic tests have proven predictive validity in the high risk infant and in comatose patients (Chiappa, 1990).

Ferry (1987) recommended that SEP be recorded in this population, due to their sensitivity to hypoxic-ischemic injuries. SEP have been used intraoperatively to monitor preserved cortical function. Coles et al. (1984) used SEP to monitor 9 infants intraoperatively, and found 3 with prolonged interwave latencies in the SEP. The authors suggest that abnormalities in the SEP were potentially indicative of global brain injury from exposure to cerebral ischemia. The same

investigators measured SEP during hypothermic CPB in 13 dogs and reported that loss of SEP was indicative of reversible cerebral ischemia, supporting the use of SEP for cerebral monitoring intraoperatively. In another center, the investigators found no changes in SEP latencies or amplitudes for temperatures ranging from 21°-25°C (Wilson et al., 1988). Findings however, were not correlated specifically to clinical status. Moreover, baseline or postoperative SEP were not reported by any of the investigators.

1.6.2 Electroencephalography: The electroencephalogram (EEG) reflects the sum of multiple factors affecting cerebral function and has been used for monitoring during pediatric OHS (Hicks & Pool, 1981; Murray et al., 1986; Russ et al., 1987). Correlations have been obtained between clinical neurologic changes and EEG abnormalities (Hauser et al., 1993; Sotaniemi 1985 & 1986; Witozska et al., 1973). Pamiglione (1965) and Harden et al. (1993) demonstrated that transient EEG changes occurred soon after cardiac surgery and concluded that these changes may be attributed to electrolyte disturbances. In one center, postoperative brain function was assessed by means of quantitative EEG analysis in 33 asymptomatic children preoperatively at 6, 11, and 44 days following OHS. The investigators concluded that an organic brain syndrome, although usually mild and transient, was a general phenomenon following surgery (Hauser et al., 1993).

Very few studies have addressed the relationship between neurologic injury and neurophysiologic monitoring. In one study, the association between EEG abnormalities and postoperative clinical status was examined in the context of a randomized clinical trial reported by Newburger et al. (1993) and Bellinger et al. (1995). Continuous EEG monitoring was carried out 2 hours before surgery,

during surgery and 48 hours post surgery. Definite clinical seizures occurred more frequently among the infants randomly assigned to the DHCA group. In addition, a longer duration of circulatory arrest was significantly associated with a higher risk of EEG seizure activity ($p=0.009$) and longer recovery times ($p<0.001$). Similarly, a longer period of arrest was significantly associated with a great release of creatine kinase ($p=0.01$). Moreover, perioperative EEG abnormalities was associated with an increased risk of possible or definite neurologic abnormalities at one year ($p=0.05$).

1.7 Pathogenesis of brain injury in children with CHD

Children with CHD are subjected to various cardiac related stresses such as chronic hypoxia, congestive heart failure, cardiac arrest and failure to thrive, which in turn may influence normal growth and development of the central nervous system (CNS). Surgical related stresses such as depth of hypothermia, duration of circulatory arrest, degree and duration of cooling, rewarming, along with related medical complications may also threaten the integrity of the developing nervous system (Bellinger et al., 1991; O'Dougherty et al., 1983). Neurologic morbidity is attributed primarily to surgical related events resulting in hypoxic-ischemic insults or cerebral embolism (Curless et al., 1994), however few studies have been able to delineate a clear association between surgery and outcome. The relative contribution of cardiac related stresses to neurologic sequelae has not been carefully examined.

Human neuropathologic studies support the hypothesis of a time-dependent effect of chronic hypoxemia on the brain. White matter gliosis has been reported in children with CHD. Schilr et al. (1984), on autopsy found that, of 161 infants with CHD who died before the age of 4 months, 39% exhibited

abnormalities in the parietal white matter. Changes predominantly in the gray matter were more common in infants over 3 months of age (Newburger, 1992). Similarly, Terplan (1976) described the histopathologic patterns of the CNS in 12 infants below 2 months of age postoperatively and concluded that distinct patterns of white matter necrosis were more frequent and widespread in these young infants when compared to non surgical cases of similar age and cardiac defect. These changes appeared to be indicative of injury to immature myelin and glial precursor cells during a period of vulnerability. He concluded that the site and type of CNS damage observed was based on similar pathogenic mechanisms in both groups, reflecting a pre-existing grave medical status prior to surgery. The author felt that this was further aggravated during the process of surgical repair. Cohen and coworkers (1990) also described similar areas of injury in 100 fatal cases, however they could not establish a relationship between nervous system pathology and severity of cardiac involvement. Half of the cases observed consisted of infants under 6 months of age suggesting the possibility of an intrauterine origin, a genetic basis and/or perinatal vulnerability. Post mortem studies on 33 subjects of less than 4 months of age revealed that infants with CHD are about twice as likely to have hypertrophic astrocytes without other morphologic abnormalities in telencephalic white matter (Gilles et al., 1973).

A wide spectrum of brain pathology has been reported in the literature in children with CHD including focal or diffuse hypoxic-ischemic changes with loss of grey or white matter differentiation, cerebral atrophy, hemorrhages, thromboembolic infarcts, acute neuronal necrosis and cerebral venous thrombosis (Terplan, 1976). These neuropathologic changes seemingly reflect the complex intraoperative, postoperative and to some extent preoperative problems including metabolic, respiratory and neurologic dysfunction in addition to poor myocardial

functioning, which collectively may result in hypoxic-ischemic encephalopathy, strokes and cardiac arrest; thus suggesting the possibility of multiple mechanisms of brain injury involvement.

A number of pathogenic mechanisms have been implicated as possible etiologies in the nervous system damage that may result following OHS. These include cerebral air or particulate emboli from CPB, loss of cerebral blood flow autoregulation, uneven cooling of the brain, hypoxic-ischemic insult due to a prolonged arrest period, 'no-reflow' phenomenon and hyperglycemia leading to excessive glycolysis. More recently, metabolic alterations in response to hypoxic-ischemic events, notably the accumulation of the glutamate neurotransmitter has been suggested to be excitotoxic in excess. In addition, impaired mitochondrial functioning during cooling or rewarming has also been proposed (Brunberg et al., 1974; Deleon et al., 1990; DuPlessis et al., 1993; Ferry, 1990; Huntley et al., 1993; Kramer et al., 1976; Newburger et al., 1993; Wical & Tomasi, 1990). In the acute postoperative phase, such disturbances may alter neurotransmitter balance and lead to the evolution of extrapyramidal changes involving primarily the basal ganglia and deep cortical structures (Wical & Tomasi, 1990). The striatum may be especially vulnerable following a history of chronic hypoxia preceding an acute surgical insult (Wong et al., 1992).

The mechanisms of brain injury in children with CHD appear to be multifaceted and likely involve the interaction of both cardiac and surgical related risk factors. Experimental and pathologic studies support the view that a series of combined and cumulative stresses may result in cerebral injury in these children.

In summary, there is increasing concern about possible neurologic sequelae in children with CHD, particularly following open heart surgery. Pre-

existing neurologic deficits prior to surgery have been suggested, however this has not been explored using detailed, standardized neurodevelopmental assessments. Although acute postoperative neurologic dysfunction has been documented, the functional impact of these findings remains sparse. Furthermore, the long-term neurodevelopmental outcome in these children remains unknown.

1.8 Rationale

Experimental studies generally support the view that induced hypothermia under total circulatory arrest imposes a risk for brain injury (Ferry, 1990; Stuart, 1994; Treasure et al., 1983). Although DHCA has been used extensively for over 30 years, resolution of the safe boundaries of this procedure remain controversial (Ferry, 1987).

Infants with complex congenital heart defects typically present in the newborn period, and will require surgical correction or palliation. Although neurologic abnormalities are now being recognized as frequent concomitants of congenital heart defects, there exists considerable controversy in the literature regarding the extent and nature of these neurologic sequelae. To date, these neurologic sequelae have been largely attributed to surgical events and procedures. There is a paucity of reports on detailed baseline examination of the central nervous system in infants and young children with congenital heart disease. The few studies that have explored whether neurologic dysfunction is present prior to surgery have either been retrospective or informal. There has only been one study describing the neonatal status of newborns with congenital heart defects reported over 20 years ago (Gillon, 1973). Although neurologic findings were not uncommon, the study did not use standardized and quantitative measures. Precise assessment and documentation of preoperative neuromotor status using comprehensive and reliable measures are lacking.

While it is increasingly appreciated that infants with congenital heart defects are at risk for neurologic sequelae, early predictors of subsequent neurologic outcome are needed. Evoked potentials may be used to objectively evaluate the integrity of the immature nervous system in newborns. Somatosensory evoked potentials have been used intraoperatively to monitor the effects of surgical

events on the integrity of the nervous system. There are no prospective studies that have ascertained baseline somatosensory evoked potentials and correlated changes in somatosensory evoked potentials with outcome. These electrophysiologic tests have proven prognostic significance in other populations sustaining insults to the CNS, including 'high-risk' neonates (Majnemer et al., 1988, 1990) and may prove to be a sensitive prognostic tool in the infant cardiac population.

This study examined the neurobehavioral status of newborns with congenital heart defects. Quantitative and qualitative clinical measures as well as electrophysiologic techniques were used to characterize central nervous system integrity in this population in the newborn period. Furthermore, newborns' neurobehavioral status was correlated with cardiorespiratory status at that time, to ascertain whether or not neurologic abnormalities merely reflect cardiorespiratory compromise or were unrelated to the degree of acute illness. It should be noted that to date, there has been no study that has formally assessed and correlated baseline cardiorespiratory status of infants with neurologic status.

2. OBJECTIVES

1. To determine the neonatal neurologic and neurobehavioral performance of newborns diagnosed with a CHD in the first month of life, and to compare the neurobehavioral performance between newborns with CHD and healthy full-term neonates.

2. To assess electrophysiologically the functional integrity of the ascending dorsal column medial lemniscal system of newborns with CHD.

3. To ascertain whether neurologic abnormalities manifesting in the neonatal period are associated with indicators of cardiorespiratory illness.

4. To determine the degree of agreement between the neonatal neurologic examination and the ENNAS in newborns with CHD.

3. METHODOLOGY

3.1 Introduction

This study was phase I of an ongoing prospective study that is examining the neurodevelopmental status of young children prior to and following OHS. Clinical and electrophysiologic tests are being carried out in the newborn period, one week prior to surgery, prior to discharge following surgery and one year later (investigators: Dr. Majnemer, Dr. Rosenblatt, Dr. Rohlicek, Dr. Shevell, Dr. Tchervenkov). In this chapter, methods of subject recruitment and subject inclusion/exclusion criteria are defined. Testing procedures are outlined and the statistical analyses are described.

3.2 Design overview

In this prospective study, a consecutive series of newborns referred to the Cardiology Department at the Montreal Children's Hospital (MCH) from September 1994 to July 1996, with a diagnosis of complex CHD necessitating palliative or corrective open heart surgery, and who were anticipated to require CPB and/or DHCA in childhood, were recruited for the study. Neurologic, neurobehavioral, electrophysiological and cardiorespiratory assessments were performed within the first month of life, prior to surgery. The vast majority of newborns were admitted to the hospital's neonatal intensive care unit, thus facilitating the scheduling and administration of the evaluative procedures. The remainder of the subjects were identified through the out-patient cardiology clinic.

3.3 Subjects

Inclusion criteria:

a. gestational age >36 weeks

b. diagnosis of a complex congenital heart defect (i.e. requiring palliative or corrective open heart surgery in childhood) in the newborn period (first month of life)

c. referred to the Cardiology Department in the newborn period

Exclusion criteria:

a. known extracardiac anomalies involving the central nervous system (e.g. Down syndrome)

b. known insult to the central nervous system (e.g. hypoxic-ischemic encephalopathy due to asphyxial injury)

3.4 Procedures

When a newborn was first referred to cardiology and subsequently diagnosed as having a CHD, the attending cardiologist briefly introduced the study to the families and upon their approval notified the occupational therapist so that she could explain the study to the parents and seek written consent from those who agreed to participate.

Once consent was obtained, the subjects were assessed soon thereafter to ensure that the evaluation was carried out in the newborn period (i.e. first month of life). The completed assessment took approximately 60-90 minutes, and included evaluations by occupational therapy, neurology, cardiology and somatosensory evoked potential testing . The Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS) was performed by two occupational therapists. Controls from the neurodevelopmental laboratory at the Montreal Children's Hospital for the ENNAS

were used to compare performance between subjects and healthy full term newborns. These healthy full term controls' were recruited from St. Mary's Hospital's well-baby nursery for a previous study (Majnemer et al., 1992). Newborns were included in this cohort if they were full term (i.e. gestational age greater than or equal to 37 weeks), with birthweights appropriate for gestational age, a 5 minute Apgar score greater than or equal to 8, and only if they experienced no perinatal complications (i.e. pregnancy or delivery).

In the current study, a pediatric neurologist assessed each subject's neurologic status and a cardiologist assessed the cardiorespiratory system. Subjects admitted to the hospital were evaluated by the OT, the cardiologist and the neurologist in the Neonatal Intensive Care Unit (NICU) at the bedside, whereas out-patients were assessed by the examiners in the clinical neurophysiology laboratory at the hospital. The occupational therapist and pediatric neurologist were blinded to the diagnosis and to the other examiner's clinical findings. For all subjects SEP recordings were performed in the clinical neurophysiology laboratory. Patients determined by the attending neonatologist to be medically too unstable to leave the NICU did not undergo SEP evaluation.

3.5 Testing Procedures

3.5.1 Neurobehavioral assessment: The Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS) was administered to all subjects by two examiners on the project. The ENNAS is a formal neurologic assessment that evaluates neurological and behavioral organization of the newborn infant. Standardized procedures and methods are used in performing each individual item, however the order of presentation of each item is such that state is optimized. For example, if the infant is in a quiet, alert state, behavioral items are

administered first; if the infant is initially sleepy, motor items are carried out first to arouse the infant. The areas evaluated include muscle tone, passive and active movements, primitive reflexes, and responses to visual and auditory stimuli. This neonatal assessment was developed by a group at Albert Einstein University to provide a reliable and comprehensive assessment of a range of clinically observable neurobehavioral features of the newborn at term (Daum et al., 1977). It incorporates test items from existing examinations that adopt two traditions, the classical neurological approach (i.e. Prechtl, 1977) and behavioral (i.e. Brazelton, 1995) assessments (Kurtzberg et al., 1979). The ENNAS is comprised of 20 items and 4 summary items and takes 20-30 minutes to administer. Interrater reliability was determined to be 0.97 by Kurtzberg et al. (1979), however the method used to obtain this value was not described. Each item is scored on an ordinal scale sequenced from minimal to maximum response (4-point scale for most items). There are no normative data for performance, however cut-offs for normal/abnormal for each of the items is based on criteria established and defined by the Einstein University group (McCarton, personal communication). A deviant score (i.e. number of items failed) between 0-2 is considered normal, whereas a deviant score between 3-6 is indicative of a suspect examination and a deviant score greater than 6 is considered abnormal for the test. On the ENNAS, healthy full-term newborns are expected to obtain a deviant score between 0-2 (McCarton, personal communication). Furthermore, clinically, neonates with neurologically 'suspect' findings demonstrate subtle or mild abnormalities (e.g. mildly hypotonic, poor orienting responses, etc.) and would be considered abnormal. An 'abnormal' exam (e.g. opisthotonic posturing, hypertonia, motor asymmetry) is reflective of a severely aberrant neurologic status. For the purpose of analysis, suspect or abnormal examinations were considered to be abnormal

and the ENNAS scores were therefore collapsed into normal/abnormal scores, where a deviant score greater than 2 (suspect score and abnormal score) was considered abnormal. Laboratory data obtained on 47 healthy term newborns demonstrated that 70% of these term babies had a deviant score of 0 or 1 and none had a deviant score greater than or equal to 3 (Majnemer et al., 1994). With respect to discriminant validity, comparison of performance on the ENNAS of healthy controls and 74 high-risk newborns (i.e. small for gestational age, very low birth weight and asphyxiated babies) demonstrated significant differences in deviant score ($p<0.001$) and on most individual test items ($p<.05$) (Majnemer et al., 1993). Predictive validity was also evaluated by the same investigators. The test demonstrates a good negative predictive value and sensitivity for developmental outcome at 1, 3, and 5 years respectively for high-risk newborns, however there are many false positives (Majnemer et al., 1994; Majnemer & Rosenblatt, 1995). Wallace and colleagues (1995) also examined the predictive validity of three aspects of the ENNAS in 144 low birth weight preterm infants, and reported that the visual follow composites from the ENNAS were significantly related to the Mental Developmental Index (MDI) and IQ scores at 1,2 and 6 years of age ($p<0.01$), and auditory composites at 1 and 6 years ($p<0.05$). Furthermore, deviant performance on both visual and auditory composites was associated with significantly lower test scores (MDI and IQ) at one and six years of age ($p<0.005$).

The occupational therapist also completed an observation data sheet that included information about the infant's perinatal status (i.e. gestational age, birth weight, Apgar score, diagnosis, etc.). General feeding status was recorded as described by the primary caregiver (i.e. nurse on the ward, or mother when the infant was seen as an out-patient) and included the method of feeding, feeding efficiency (i.e. amount of intake, duration of feeding, need for nasogastric

supplementation). Abnormalities in state regulation (i.e. lethargy, excessive irritability/agitation, inability to maintain a quiet alert state) during the ENNAS, muscle tone and the overall impression regarding the infant's neurobehavioral status were also documented following the assessment (Appendix A).

3.5.2 Neurologic examination: A pediatric neurologist examined all subjects based on criteria outlined by Volpe (1995). The examination took approximately 15 minutes and included assessment of head circumference, muscle bulk and tone, cranial nerves, deep tendon reflexes, activity level and the presence of any abnormal movement patterns such as posturing or tremor. Subjects were categorized into a normal/abnormal dichotomy based on the results of the neurologic exam (Appendix B).

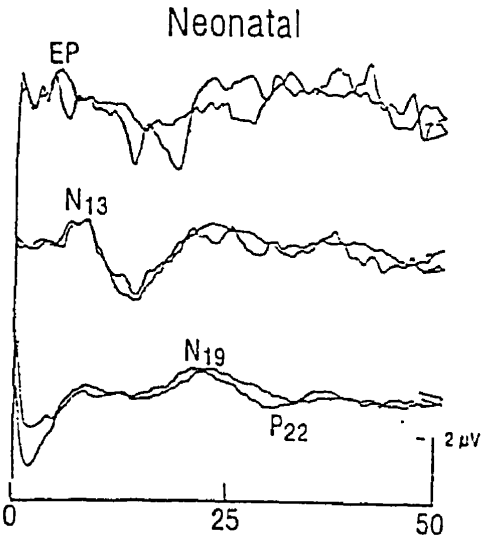
3.5.3 Electrophysiologic testing: Somatosensory evoked potential (SEP) testing was administered by a technician from the hospital's clinical neurophysiology laboratory. Gold cup electrodes were applied with electrode paste to the following measurement sites: Erb's Point (EP), over the second cervical vertebra (N13) and on the contralateral parietal scalp (N19), 2 cm behind C3 and C4 (as defined by the 10-20 system). The montage selected produced negativity in an upward direction for all peaks. An electrical square-wave pulse was delivered to each median nerve using an infant-stimulator at a rate of 4 Hz, a duration of 0.2 milliseconds, and an intensity sufficient to produce a minimal thumb twitch. Resistance was maintained below 5 kohm. Bandpass filters were set at 30-3000 Hz, and recordings were amplified 100,000 times. A trial was defined as 512 responses that were averaged and recorded. Two trials of 512 responses

were performed (immediate test-retest), superimposed, and plotted out as waveforms to determine waveform reproducibility. Absolute latencies (i.e. EP, N13, N19) or interwave latencies (i.e. N13-N19, N19-N22) falling greater than 2.5 standard deviations of age-matched normative data were considered as abnormal (Appendix C). Therefore, an abnormal SEP recording in a newborn would be characterized by either i) latencies of the N19 peak that are greater than 2.5 standard deviations (mean: 25.0 milliseconds, standard deviation: 2.91) of age-matched controls (i.e. slow central conduction time), ii) increased N13-N19 interwave latencies (mean: 15.1 milliseconds, standard deviation: 2.68) or iii) bilateral absent parietal potentials (N19) (Laureau et al., 1988) (Figure 1). Unilateral absence has been recognized in a small percentage of healthy full term newborns, and therefore cannot be considered abnormal in the newborn period. The SEP results were compared to normative data, established on control subjects at the Montreal Children's Hospital clinical neurophysiology laboratory with regards to the peak latencies and interwave latencies. Guidelines for wave form identification followed criteria established by Majnemer and Rosenblatt at the laboratory (unpublished manuscript). Absolute and interwave latencies were measured by two independent readers. Findings were then discussed between readers to clarify any discrepancies, and determination made as to whether the findings were normal or abnormal.

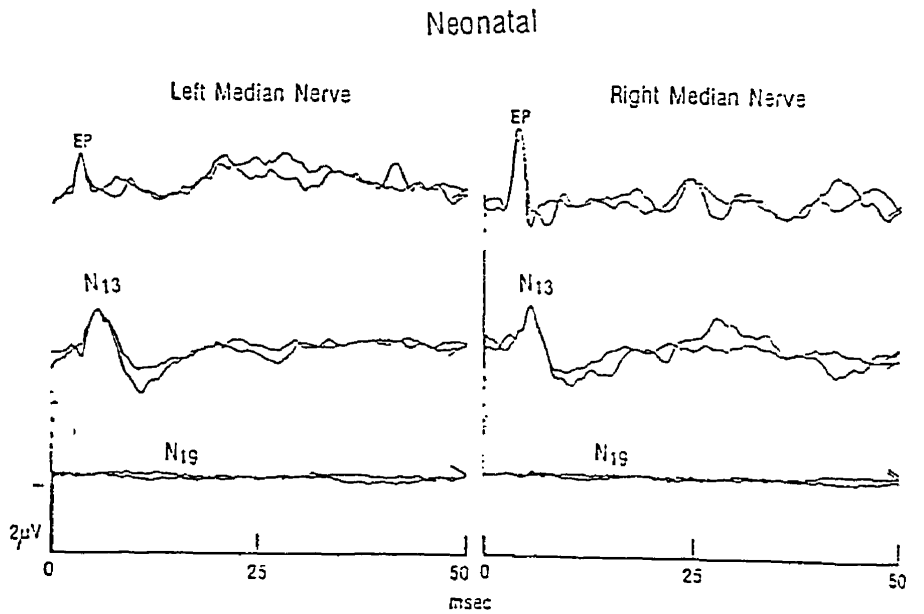
Regarding the psychometric properties of this test, studies have shown good predictive validity with sensitivity, specificity and predictive values ranging from 80-100% for early neuromotor outcome in asphyxiated full term infants (Majnemer et al. 1990 & 1995). Furthermore, interrater reliability for an SEP

Figure 1: An example of a normal (a) and abnormal (b) SEP recording in newborns

(a) A normal SEP recording in a newborn is characterized by an identifiaale EP, N13, and N19 potential.



(b) An abnormal SEP recording in a newborn characterized by identifiable EP and N13 potentials, but bilateral absense of N19 potenitals.



pattern abnormality in a sample of 76 normal and head injured subjects was very good with an r value of .88 for both populations ($p<.01$) (Rappaport et al. 1981). Test-retest reliability was examined in a second study on 28 normal subjects, with high correlation coefficients for reproducibility of waveform latencies, ranging from .96 - .98 (Kresch et al. 1992).

3.5.4 Cardiorespiratory status: A cardiologist on the project examined each subject and scored the overall cardiorespiratory status. Areas documented included: oxygen saturation, respiratory rate, whether newborns were intubated, on prostaglandins, and the presence of cyanosis and/or congestive heart failure (Appendix D). The cardiologist also documented whether the subjects were evaluated as in or out patients, as presumably out patients would be more stable from a cardiorespiratory view point. These parameters were used as indicators of cardiorespiratory compromise, and were correlated to neurobehavioral status to determine if poor neurobehavioral performance was merely reflective of acute medical illness.

3.6 Statistical Analysis

Objective #1 To describe the neonatal neurologic and neurobehavioral performance of newborns with CHD:

Descriptive statistics were used to characterize perinatal characteristics of newborns with CHD including: gestational age at birth, conceptional age at testing, Apgar scores at 1 and 5 minutes, birthweight, number of male/female infants, diagnosis and any secondary diagnosis. Descriptive statistics were also used to determine the proportion of children demonstrating abnormalities on the

ENNAS and the neurologic examination. Performance between subjects with CHD and laboratory controls (healthy full-term newborns) was compared for the overall deviant score classified as normal or abnormal, and for individual items on the ENNAS using chi square analysis. The Mann-Whitney test was used to compare the distribution of scores on each item between the above groups in order to determine if there were any significant differences. Chi square analyses (i.e. normal vs. abnormal) were also carried out to examine the relationship between the ENNAS deviant score and the neurologic examination.

Objective #2 *To describe SEP findings in newborns with CHD:*

SEP produce continuous, normally distributed data which can be categorized as normal or abnormal (i.e. >2.5 standard deviations beyond the mean of laboratory age-matched controls). Descriptive statistics were used to indicate the number of subjects with abnormal SEP, and to characterize the type of abnormality (e.g. absent potential versus conduction delay).

Objective #3 *To determine whether neurobehavioral abnormalities in newborns with CHD association with the degree of cardiorespiratory illness:*

Chi square analyses (i.e. Fisher's Exact Test) were used to evaluate the relationship between the various cardiorespiratory factors (i.e. oxygen saturation, respiratory rate, congestive heart failure, intubation, treatment on prostaglandins, cyanotic versus acyanotic CHD) and neurobehavioral performance on the ENNAS (normal/abnormal).

Objective #4 *To examine the relationship between performance of newborns with CHD on the neonatal neurologic examination and the ENNAS:*

Chi square analyses were carried out to examine the concurrent validity between the ENNAS deviant score (i.e. score >2 is abnormal) and the results of the neonatal neurologic examination (normal/abnormal). Crude agreement was derived which represents the proportion of observations on which there is agreement. A Kappa statistic was used to measure the strength of the relationship between the two different assessments.

Sample size calculation:

Sample size calculations were based on statistical considerations, on clinical reality and on the concept of single proportions (Colton, 1974). Based on pilot data and previous reports in the literature, the prevalence of neurologic abnormalities in this population was estimated at approximately 50%. A number of sample size calculations were made (Table 1). Using a sample size of 42, the confidence interval may be estimated to be within ± 15% precision of the true population percent. Using a sample size of 95, we could further reduce the confidence interval to within a ± 10% precision. Based on the admissions rates to the Montreal Children's Hospital during the study period, it was realistic to anticipate achieving a sample size of 45 during a 12-18 month period.

Table 1: Estimates based on varying sample sizes

n = 24	-	width	=	20%	+	= 50
n = 42	-	width	=	15%	+	= 50
n = 95	-	width	=	10%	+	= 50

3.7 ETHICS

A consent form (Appendix E) was drafted describing the study using clear and simple language to obtain informed consent from a parent for their child's participation in the study. The consent form specified the nature of the research project, the various testing procedures, the freedom to withdraw from the study at any time without penalty, the assurance of confidentiality, and an offer to answer any questions and to provide further information if requested. There are no known risks associated with these testing procedures. This research project was approved by the Scientific Review Committee and the Institutional Review Board of the Montreal Children's Hospital and the Quebec Minister of Social Affairs.

4. RESULTS

4.1 Introduction

In this chapter the main results of the study are presented. Important characteristics of the cohort are described in section 4.2. Analyses of test performance of newborns with CHD is then presented in section 4.3. Comparison of performance on the ENNAS between subjects and healthy full-term controls is described in section 4.4 and somatosensory evoked potential results are summarized in section 4.5. Analyses were conducted to examine the relationship between neurobehavioral abnormalities and cardiorespiratory status in newborns with CHD and these results are discussed in section 4.6, and comparison of neurologic findings between the occupational therapist and the pediatric neurologist are presented in section 4.7.

4.2 Group characteristics

Forty-nine families were approached for consent, and 45 (91.8%) agreed to participate in the study. Descriptive statistics were carried out to characterize the perinatal status of the cohort (Table 2). Of the 45 subjects recruited, 19 (42.2%) were females and 26 (57.8%) were males. All subjects were full term newborns with birthweights appropriate for gestational age in all but one subject. Apgar scores at 5 minutes ranged from 7-10 in all subjects, except for 1 subject with an Apgar score of 4. Eight of 45 (17.7%) subjects were evaluated as out patients while the remainder were assessed in the neonatal intensive care unit. Subjects fell into various diagnostic categories of congenital heart defects including

transposition of the great arteries (TGA) (n=7), transposition of the great arteries with a ventricular septal defect (n=2), tetralogy of fallot (n=5), tetralogy of fallot with pulmonary atresia (n=5), ventricular septal defect (n=3), atrial ventricular septal defect (n=1), univentricular heart (n=2), truncus arteriosis (n=1), aortic stenosis (n=2), aortic stenosis with coarctation (n=1), interrupted aortic arch (n=1),coarctation of the aorta (n=1), coarctation of the aorta with a ventricular septal defect (n=3), coarctation of the aorta with transposition of the great arteries (n=1), complex (n=3), double outlet right ventricle (n=3), double outlet right ventricle with tetralogy of fallot (n=3), and 1 subject with total anomalous pulmonary venous drainage.

Table 2
Perinatal characteristics of newborns with CHD (N=45)

DESCRIPTIVE STATISTICS	GESTATIONAL AGE (weeks)	BIRTH WEIGHT (grams)	APGAR (1 minute)	APGAR (5 minute)
Mean	39.2	3279.3	6.8	8.3
Standard Deviation	1.3	588.6	1.9	1.3
Range (minimum)	37.0	2295.0	2.0	4.0
Range (maximum)	41.0	5150.0	10.0	10.0
Median	40.0	3250.0	7.5	9.0

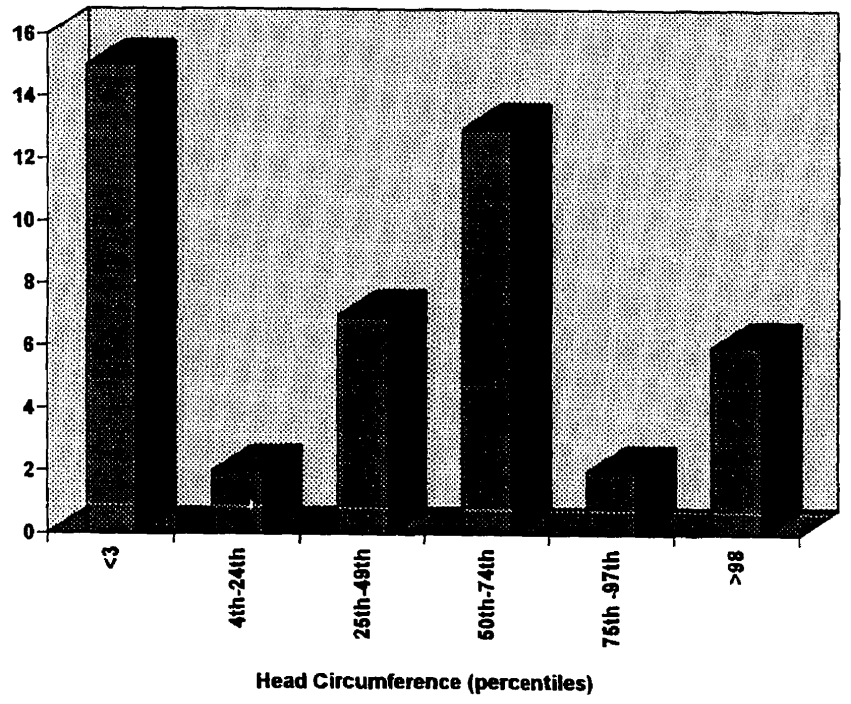
4.2.1 CARDIORESPIRATORY CHARACTERISTICS: Cardiorespiratory status was documented by the cardiologist on all 45 newborns at the time of neurobehavioral assessment. Seven (15.6%) subjects were intubated and

ventilated, 2 (4.4%) subjects were receiving supplemental oxygen through nasal prongs, while the remainder (80.0%) were in room air. Thirty-one newborns (68.9%) were cyanotic, and 14 (31.1%) were acyanotic. Nine subjects (20.0%) were in congestive heart failure, and 14 (31.1%) were tachypneic (i.e. respiratory rate greater than or equal to 55). Twelve (26.6%) subjects were not receiving any medications; whereas 19 (42.2%) were on prostaglandins, 3 (6.7%) lasix, 3 (6.7%) on prostaglandins and lasix, 3 (6.7%) on lasix and digoxin, 1 (2.2%) prostaglandins, lasix and digoxin, 1 (2.2%) prostaglandins and fentanyl, 1 (2.2%) digoxin, lasix and hydrochlorothiazide, 1 (2.2%) prostaglandins, ampicillin, gentamycin, and 1 (2.2%) hydrochlorothiazide and spronolactone. Each of these indicators of cardiorespiratory status were not mutually exclusive (i.e. newborns could fall under more than one category such as tachypnea and congestive heart failure).

4.3 Description of test performance of newborns with CHD

4.3.1 Neurologic examination: Forty out of 45 subjects were examined by a pediatric neurologist at a mean age of 13.9 +/- 11.8 days (range: 1-44 days). Fifty percent (20/40) demonstrated one or more abnormal neurologic findings including; hypotonia (n=13), hypertonia (n=3), opisthotonia (n=1), jitteriness (n=3), no suck (n=3), motor asymmetry (n=2), seizures (n=2), decreased muscle power in the upper and lower extremities (n=2), and cranial nerve abnormalities (n=2). Altered states of consciousness were also documented, and consisted of lethargy and stupor (n=6), as well as restlessness and agitation (n=2). In addition, microcephaly (i.e. head circumference at or below the third percentile) was documented in 33.3% (n=15) of subjects. Interestingly, 13.3% (n= 6) of newborns with CHD were macrocephalic (Figure 2).

Figure 1: Distribution of head circumference in newborns with CHD



4.3.2 ENNAS: The ENNAS was carried out by an occupational therapist on 41/45 subjects at a mean age of 13.0 +/- 11.3 days (range: 2-44 days). Eighteen (43.9 %) subjects had a normal examination (i.e. deviant score 0-2), 17 neonates (43.9%) obtained a deviant score between 3-6 indicating a suspect examination, and 6 (14.6 %) had an abnormal ENNAS (i.e. deviant score greater than 6). Abnormalities observed and recorded on suspect or abnormal ENNAS examinations (i.e. deviant score >2) included hypotonia (n=15), jitteriness (n=4), hypertonia (n=4), no suck (n=3), motor asymmetry (n=2), and opisthotonus (n=1). Poor orienting responses were often observed, which consisted of poor visual fixation and tracking (13/26) as well as poor auditory alerting (31/34). Furthermore, poor state regulation was documented in 60.9% (n=25) of subjects following completion of the ENNAS. This was characterized by lethargy and inability to arouse and maintain an optimal state of arousal (n=11), and/or excessive irritability and abrupt swings between sleep and crying states with no quiet alert periods (n=14). The poor state regulation frequently observed in the cohort made testing of orienting responses difficult, and at times, impossible.

4.3.3 FEEDING: Out of the 45 subjects, 24 were fed orally (breast or bottle), 4 required nasogastric supplementation and 17 were on total parentral feedings. Eleven (26.8%) subjects had a weak non-nutritive suck and 3 had no suck as documented on the ENNAS (item #4). All newborns with a weak non-nutritive suck were also found to be hypotonic on neurobehavioral assessment. Feeding efficiency was documented informally on subjects that were fed orally, based on information provided by the primary caregiver (e.g. primary nurse or mother) regarding the infants' feeding behaviors. Decreased feeding efficiency was

subjectively described in 33.3% (n=15), which was characterized by insufficient intake necessitating a longer feeding time and frequent feedings to ensure adequate oral intake and sufficient weight gain.

In summary, neurobehavioral findings were documented in approximately half the subjects by both the occupational therapist (56%) and the pediatric neurologist (50%) and consisted of: tone and movement abnormalities, motor asymmetry, seizures, poor orienting responses, poor state regulation, and feeding difficulties including weak or no suck and decreased feeding efficiency. Microcephaly was documented in one third of subjects.

4.4 Comparison of Performance on the ENNAS between subjects and healthy control group

The Neurodevelopmental Laboratory at the Montreal Children's Hospital has evaluated 47 healthy full term babies using the ENNAS (Majnemer et al., 1992). Two statistical procedures were applied to compare test performance on the ENNAS between newborns with congenital heart defects and full-term laboratory controls.

First, each test item was categorized as normal or abnormal, using criteria established by Kurtzberg et al. (1979). Chi square analyses (i.e. Fisher's Exact Test) were used to compare the performance (normal or abnormal) on each test item between subjects and controls. There were significant differences in test performance on several subtests, including orienting responses (both visual and auditory subtests) ($p<0.0001$), passive and active movements including arm recoil, ($p<0.0001$), head extension ($p<0.05$), upper limb traction ($p<0.05$), head lag ($p<0.05$), active head extension ($p<0.05$), extremity movement ($p<0.05$),

cuddliness ($p<0.0001$) and muscle tone ($p<0.0001$) (Table 3 and Table 4). Lateral position preference, popliteal angle, rooting, sucking, grasp, moro, withdrawal, tonic neck reflex, ventral suspension, rotation and the presence and incidence of tremor were not significantly different between healthy and high risk groups ($p>0.05$).

The Mann-Whitney test is a nonparametric version of the two group unpaired t-test. It was used to compare the distribution of scores for items on the ENNAS between the subjects and controls. This analysis tests the hypothesis that the distribution of scores for each item on the ENNAS underlying the two groups is the same. Not surprisingly, significant differences in the distribution of scores were documented in the majority of items (Table 3), with the exception of the following items: lateral head preference (which evaluated head position in supine at rest), popliteal angle (which determines the degree of flexion at the knees), tonic neck reflex, rotation (post rotatory nystagmus) and the presence of tremor (Figures 3 and 4).

In summary, comparison of performance on the ENNAS between subjects and healthy controls demonstrated significant differences in test performance (e.g. normal/abnormal) on many individual test items, as well as in the distribution of scores for items. These included orienting responses (both visual and auditory subtests), passive and active movements, as well as muscle tone, cuddliness and extremity movements.

TABLE 3
Comparison of performance on the ENNAS between newborns with CHD and controls

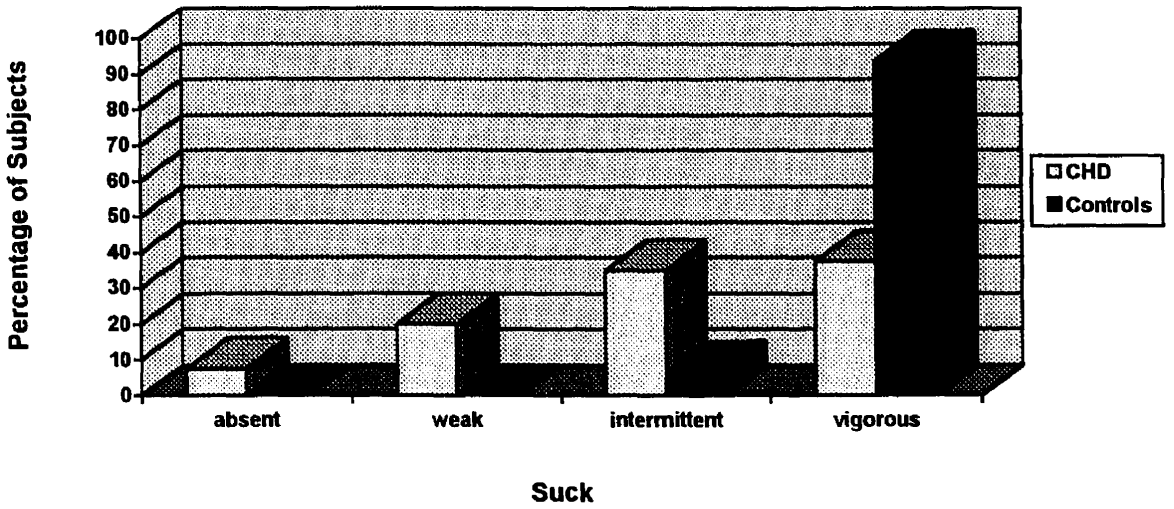
ENNAS (items)	CLASSIFICATION OF SCORES: normal/abnormal (Fisher Exact Test)	DISTRIBUTION OF SCORES (Mann-Whitney Test)
ORIENTING ITEMS		
Visual follow	0.0001*	0.0001*
Auditory alerting	0.0001*	0.0001*
REFLEXES		
Rooting	0.59	0.0001*
Sucking	0.09	0.0001*
Grasp	0.99	0.0001*
Moro	0.59	0.0001*
Withdrawal	--	0.0001*
Tonic neck reflex	0.99	0.10
Rotation	0.99	0.35
PASSIVE & ACTIVE MOVEMENTS		
Lateral position preference	--	0.11
Popliteal angle	0.59	0.58
Arm recoil	0.0001*	0.001*
Head extension	0.01*	0.0001*
Traction	0.04*	0.0001*
Head lag	0.04*	0.0001*
Active head extension	0.02*	0.0001*
Extremity movements	0.03*	0.0001*
Ventral suspension	0.06	0.0001*
SUMMARY ITEMS		
Cuddliness	0.0001*	0.0001*
Spontaneous movements	0.09	0.0001*
Tremor	0.37	0.70
Muscle tone	0.0001*	0.001*

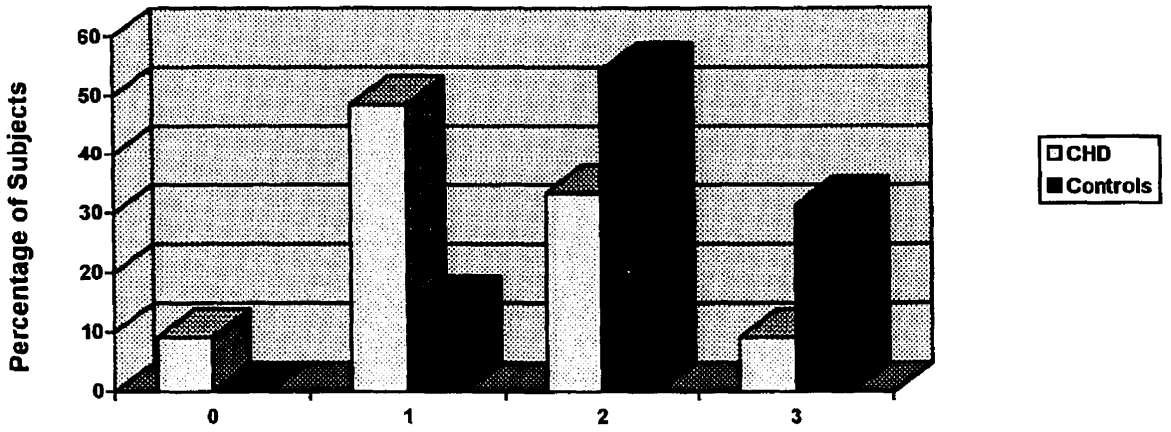
* Significant differences

Table 4
Comparison of the proportion of abnormalities on the ENNAS between newborns with CHD and controls

ENNAS (items)	Newborns with CHD (% with abnormalities)	Controls (% with abnormalities)
ORIENTING ITEMS		
Visual follow	52.0	24.0
Auditory alerting	90.3	19.6
REFLEXES		
Rooting	4.8	2.1
Sucking	7.5	0.0
Grasp	2.7	2.1
Moro	4.9	2.1
Withdrawal	--	--
Tonic neck reflex	2.4	2.1
Rotation	0.0	0.0
PASSIVE & ACTIVE MOVEMENTS		
Lateral position preference	--	--
Popliteal angle	4.9	2.1
Arm recoil	62.5	12.5
Head extension	14.7	0.0
Traction	19.5	4.2
Head lag	37.8	10.4
Active head extension	12.5	0.0
Extremity movements	12.1	0.0
Ventral suspension	9.1	0.0
SUMMARY ITEMS		
Cuddliness	36.1	2.1
Spontaneous movements	7.3	0.0
Tremor	11.1	18.7
Muscle tone	50.0	0.0

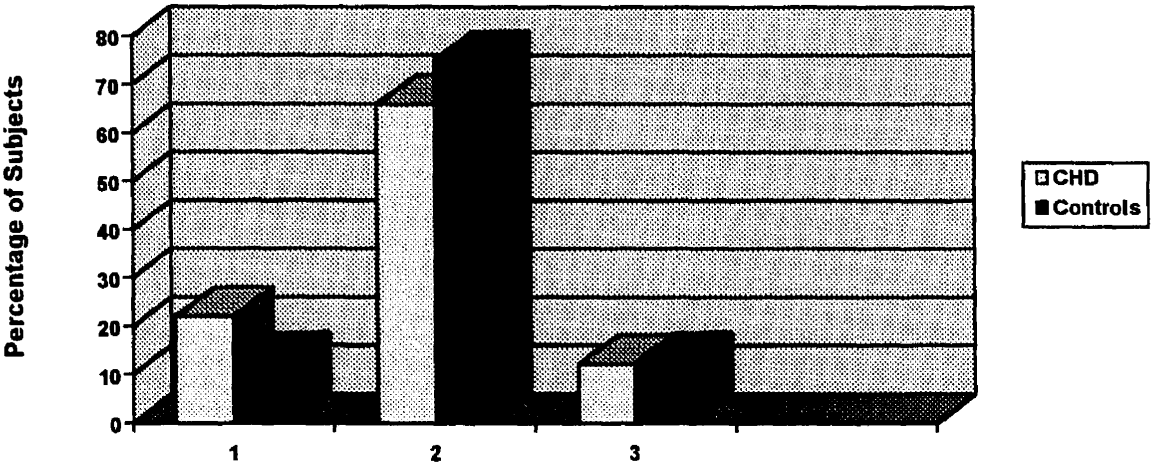
Figure 3: Examples of significantly different distributions between subjects and controls on two items on the ENNAS





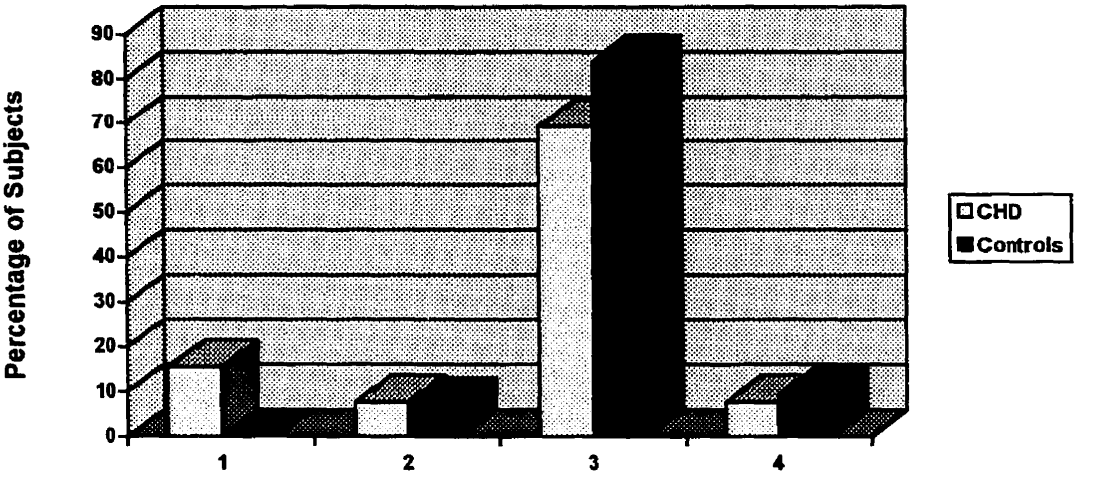
0= flaccid, 1=some extremity flexion, 2= transient head lifting and extremity flexion, 3= sustained head lifting and extremity extension

Figure 4: Examples of similar distributions between subjects and controls on two items on the ENNAS



Popliteal angle

0= 150-180 degrees, 1= 120-150 degrees, 2= 90-120 degrees, 3= <90 degrees



Rotation

0=no ocular response, 1= lateral deviation, 2=lateral deviation and post-rotational deviation to opposite side, 3= lateral deviation and post-rotatinal nystagmus, 4= nystagmus during rotational

4.5 Somatosensory evoked potential findings in newborns with CHD

Somatosensory evoked potential (SEP) recordings following median nerve stimulation were obtained on only 15 subjects given that the remainder of subjects were not stable enough to be transported off the unit to the clinical neurophysiology laboratory. Thirteen subjects demonstrated normal SEP recordings, while 2 subjects had abnormal findings which consisted of bilateral absent N19/P22 cortical potentials.

4.6 Relationship between neurobehavioral abnormalities and cardio-respiratory status

Chi square analyses were carried out to examine the relationship between individual cardiorespiratory factors and neurobehavioral performance on the ENNAS (Table 5 & Table 6). Analyses demonstrated a significant association between neurobehavioral status (deviant score of the ENNAS), and cyanotic versus acyanotic congenital heart defects, where newborns with acyanotic congenital heart defects were more likely to be neurologically abnormal than those with cyanotic defects. However, there was no significant association ($p>.05$) between neurobehavioral performance and any indicators of cardiorespiratory compromise (e.g. the presence of congestive heart failure, tachypnea, oxygen saturation, treatment of prostaglandins, intubation, or in versus out patients). Furthermore, an unpaired t-test showed no significant association ($p=0.19$) between oxygen saturation in those subjects with normal deviant scores (mean oxygen saturation: 88.2% +/- 8.4) and those with abnormal ENNAS (mean oxygen saturation 91.0% +/- 8.0).

Table 5
Relationship between cardiorespiratory factors and ENNAS score

Cardiorespiratory Factors	P value (Fisher Exact Test)
Congestive heart failure	0.27
Tachypnea (respiratory rate>55)	0.99
Oxygen saturation (<85)	0.51
Cyanotic vs. acyanotic	0.04 *
Ventilated	0.99
Prostaglandins	0.99
In vs. out-patient	0.99

* significant difference

Table 6
Summary tables of ENNAS deviant score and cardiorespiratory factors

ENNAS	**Respiratory Rate (normal)**	**Respiratory Rate (tachypnea)**	Total
Normal	9	6	15
Abnormal	13	7	20
Total	22	13	35

Fisher Exact Test (p=.99)
(6/41 were intubated)

ENNAS	**Room Air (not intubated)**	**Intubated & Ventilated**	Total
Normal	15	3	18
Abnormal	20	3	23
Total	35	6	41

Fisher Exact Test (p=.99)

ENNAS	**Oxygen Saturation › 85%**	**Oxygen Saturation ‹ 85%**	Total
Normal	11	7	18
Abnormal	17	6	23
Total	28	13	41

Fisher Exact Test (p=.51)

ENNAS	**Congestive Heart Failure (absent)**	**Congestive Heart Failure (present)**	Total
Normal	13	5	18
Abnormal	20	3	23
Total	33	8	41

Fisher Exact Test (p=.27)

ENNAS	**Prostaglandins (no)**	**Prostaglandins (yes)**	Total
Normal	8	10	18
Abnormal	11	12	23
Total	19	22	41

Fisher Exact Test (p=.99)

ENNAS	**Cyanotic Heart Defects**	**Acyanotic Heart Defects**	Total
Normal	15	3	18
Abnormal	12	11	23
Total	27	14	41

Fisher Exact Test (p=.04*)

4.7 Agreement between the neonatal neurological examination and the ENNAS in newborns with CHD

The results of the neonatal neurologic examination (performed by a pediatric neurologist) and the ENNAS (carried out by an occupational therapist) were compared to determine the degree of agreement between the two assessments. Out of the forty-five subjects, thirty-seven were independently assessed both by the pediatric neurologist and the occupational therapist. Both examiners independently evaluated each subject, and were blinded to the diagnosis, perinatal status and to each other's clinical findings. Chi square analyses were carried out to examine the relationship between the ENNAS deviant score and the results of the neonatal neurologic examination (normal/abnormal). The ENNAS and the neonatal neurologic examination were performed on the same day or following day in 34/37 subjects. The remaining three subjects were evaluated 2, 3 and 23 days apart respectively. Eighteen neonates were determined to be normal and 18 abnormal by both examiners, with disagreement in only 1 subject. Statistical analysis demonstrated a significant association (Fisher's Exact P value <0.001) between the overall impression between the two assessments (Table 7). Crude agreement, which represents the proportion of observations on which there is agreement (Portney & Watkins, 1993), was determined to be 97.3% (18+18/37). Kappa, a chance-corrected measure of agreement (Portney & Watkins, 1993), was 0.94 with a confidence interval of 0.84-1.0, indicating excellent agreement between the two tests.

Upon completion of the assessments, both examiners specifically documented abnormalities in muscle tone, symmetry, quality of movement (i.e. jitteriness), absent suck and behavioral state regulation (Table 8). There was

complete agreement in the documentation of an asymmetry (n=2), and the absence of a sucking reflex (n=3). Furthermore, both examiners independently documented that the same 21 newborns had normal muscle tone, whereas 11 were determined to be hypotonic, 3 hypertonic, and 1 opisthotonic, with an additional subject noted to be slightly floppy only by the occupational therapist. Jitteriness was seen in 3 subjects by both examiners, and additionally, upper extremity tremor was further reported in 1 newborn by the occupational therapist. Poor behavioral state regulation which was characterized by marked lethargy or irritability was recorded in 8 subjects by both examiners, and an additional 13 neonates demonstrated poor state control on neurobehavioral assessment by the occupational therapist (Limperopoulos et al., submitted).

Table 7
Agreement between ENNAS deviant score and the neonatal neurologic examination overall score (N=37)

ENNAS	NEONATAL NEUROLOGIC EXAMINATION		TOTAL
	normal	abnormal	
normal	18	0	18
abnormal	1	18	19
total	19	18	37

Chi-square = 28.2, df = 1

Fisher Exact Test p<.0001

Table 8
Comparison of findings on the ENNAS and the neonatal neurologic examination on each subject assessed by both examiners

	OVERALL SCORE	TYPE OF ABNORMALITIES							
SUBJECT NUMBER	ENNAS NEURO	Normal tone	Hypo-tonia	Hyper-tonia	Opistho-tonia	Asym-metry	No suck	Jittery	Poor state
001	normal	+						+	
	normal	+						+	
002	normal	+							
	normal	+							
003	normal	+							
	abnormal		+						+
004	abnormal			+					
	abnormal			+					+
005	normal	+							
	normal	+							
006	abnormal		+						
	abnormal		+						+
007	normal	+							
	normal	+							+
008	abnormal	+							
	abnormal	+							+
009	abnormal	+						+	+
	abnormal	+						+	+
010	normal	+							
	normal	+							
011	abnormal				+	+			+
	abnormal				+	+			+
012	abnormal	+							+
	abnormal	+						+	+
013	abnormal			+				+	+
	abnormal			+				+	+
014	abnormal		+						
	abnormal		+						
015	normal	+							
	normal	+							
016	normal	+							
	normal	+							+
017	normal	+							
	normal	+							+
018	abnormal		+						
	abnormal		+						+
019	normal	+							
	normal	+							+
020	abnormal		+				+		+
	abnormal		+				+		+
021	abnormal		+						
	abnormal		+						
022	normal	+							
	normal	+							+
023	abnormal		+						
	abnormal		+						+

	OVERALL SCORE	TYPE OF ABNORMALITIES							
SUBJECT NUMBER	ENNAS NEURO	Normal tone	Hypo-tonia	Hyper-tonia	Opistho-tonia	Asym-metry	No suck	Jittery	Poor state
024	abnormal		+				+		+
	abnormal		+				+		+
025	normal	+							
	normal	+							
026	normal	+							
	normal	+							
027	abnormal			+			+		+
	abnormal			+			+		+
028	normal	+							
	normal	+							
029	abnormal		+						
	abnormal		+						+
030	normal	+							
	normal	+							
031	normal	+							
	normal	+							
032	abnormal		+			+			
	abnormal		+			+			
033	normal	+							
	normal	+							
034	normal	+							
	normal	+							+
035	normal	+							
	normal	+							
036	abnormal		+						
	abnormal		+						+
037	abnormal		+						+
	abnormal		+						+

ENNAS = Einstein Neonatal Neurobehavioral Assessment Scale
NEURO = Neonatal Neurologic Examination
\+ = present

5. DISCUSSION

5.1 Introduction

Considerable controversy exists with regards to the integrity of the immature nervous system in newborns with CHD who undergo cardiac surgery. To date, neurodevelopmental sequelae in children with CHD have been primarily assumed to be related to surgical events. Very few studies have explored whether neurologic dysfunction is evident prior to surgery.

The objective of this study was to determine if newborns with congenital heart defects demonstrate abnormalities in neurobehavioral status in the neonatal period prior to surgery. The neurologic and neurobehavioral performance of this cohort was determined using quantitative and qualitative measures as well as electrophysiologic tests. The relationship between cardiorespiratory status and neurobehavioral abnormalities was addressed. The following chapter summarizes the main findings of the study and describes the clinical relevance and implications of these findings. Finally, limitations of the study as well as potential sources of bias are discussed, and suggestions for future studies are made.

5.2 Neonatal neurobehavioral status of newborns with CHD

The results of this study demonstrated that neurobehavioral abnormalities were common in newborns with CHD prior to open heart surgery. Neurobehavioral findings were characterized by seizures, muscle tone abnormalities, motor asymmetries, jitteriness, and poor orienting responses. In

addition, microcephaly was documented in over one third of newborns with CHD. Poor state regulation was prevalent in the sample. Feeding patterns were often abnormal, and were characterized primarily by poor suck and decreased feeding efficiency. Interestingly, the overall likelihood of neurobehavioral abnormalities was not enhanced by the presence of cardiorespiratory compromise.

Previous evidence of preoperative neurodevelopmental sequelae in infants has been documented by very few clinical investigators. Blackwood et al. (1986) examined 36 children under 2 years of age prior to surgery, and abnormalities documented included microcephaly (n=5), hemiparesis (n=4), and hypotonia (n=1). Similarly, Brunberg and colleagues (1974) carried out preoperative neurologic examinations on 21 subjects (age ranging from 4 days to 24 months) and report hypotonia in 43%, psychomotor delay in 62%, and seizures and motor asymmetry in 1 subject. Newburger et al. (1993) also performed baseline neurologic examinations in 171 infants under three months of age and reported suspect neurologic findings in 20% of their cohort and 40% with definite neurologic abnormalities, however the type of abnormalities were not described.

The only study describing the preoperative neurobehavioral status of newborns with CHD was reported over 20 years ago by Gillon (1973) who summarized her clinical observations while caring for 82 newborns prior to surgery. The author similarly documented tone abnormalities (i.e. hypotonia in 15, hypertonia in 4), restlessness (n=15), lethargy (n=22), and poor attentiveness to stimuli (n=26). In addition, feeding difficulties were noted in 63 subjects and consisted of poor suck, decreased efficiency during feeding and poor coordination of sucking, swallowing and breathing.

Human neuropathologic studies have also provided evidence of CNS injury in the acute newborn period. Terplan (1976) described distinct patterns of white matter necrosis in infants under two months of age in both surgical and non surgical cases, indicative of immature myelin and glial precursor cell injury. Although CNS involvement was more frequent in the surgical group, the author concluded that the location and type of CNS injury resulted from similar pathogenic mechanisms in both groups, indicating a pre-existing grave medical status prior to surgery which may be further exacerbated by surgery. Similarly, Schilr et al. (1984) demonstrated parietal white matter involvement in 39% of infants with CHD under 4 months of age. Cohen and colleagues (1990) also characterized comparable CNS injury sites, where half the cases were under 6 months of age. He suggested that the early brain injury may potentially be of intrauterine origin, a genetic aberration and/or perinatal vulnerability. Gilles et al. (1982) described hypertrophic astrocytes in telencephalic white matter. According to the author, these findings may in part account for an increased frequency of microcephaly in children with CHD. The mechanisms of brain injury and the reported neuropathologic changes in young infants with CHD reflect the summed effects of a combination of events resulting in CNS injury. Clinical manifestation of this acute insult to the immature nervous system may be characterized by the neurobehavioral abnormalities documented in our cohort.

The effect of cardiovascular surgical techniques used in open heart surgery on subsequent neurodevelopmental outcome has been difficult to ascertain given that children with CHD are exposed to multiple risk factors for brain injury including, chronic hypoxemia, congestive heart failure, poor nutrition,

polycythemia, brain abscess, episodes of arrhythmia or cardiac arrest, as well as other system anomalies (Bellinger et al., 1991). Pre-existing lesions or conditions may be exacerbated by sustaining additional insults during the operative procedure and may place young infants at further risk for neurodevelopmental sequelae (Park, 1984).

These acute neurologic findings appear to have a multifactorial etiology and are likely attributed to cardiorespiratory factors, medical and prenatal factors, congenital brain malformation, diagnostic and operative procedures, possible genetic predisposition and the individual adaptive capacity of the child.

5.3 Specific clinical findings

5.3.1 MUSCLE TONE ABNORMALITIES: Hypotonia is the most prevalent motor abnormality observed in neonatal neurological disorders, while hypertonia is not as common a feature (Volpe, 1995). Hypertonia in the neonatal period is typically observed with severe perinatal or intrauterine hypoxic-ischemic cerebral injury, bacterial meningitis, and massive intraventricular hemorrhage. Hypoxic-ischemic encephalopathy is by far the most common cause of hypotonia in the newborn period. Metabolic disturbances such as abnormal increases or decreases in electrolyte levels, acidemia, hypoglycemia, endocrine disorders including hypothyroidism, aberrations of brain development or chromosomal abnormalities may also result in hypotonia (Volpe, 1995).

In our cohort, tone abnormalities were documented in approximately half of the subjects and primarily consisted of hypotonia. Hypertonia was noted in 3 newborns by the neurologist and in 4 by the OT, and opisthotonis posturing in 1.

The hypotonia observed in this group is likely due to one of two major pathogenic mechanisms. Hypoxemia, which is a diminished amount of oxygen in the blood supply, is a hallmark feature of cyanotic heart disease. Secondly, ischemia, which is a diminished amount of blood perfusing the brain, may result from brief periods of variable fluctuations and diminuations of blood flow in acutely ill newborns with congenital heart defects. Ischemia and the subsequent period of reperfusion is clearly associated with deleterious consequences on brain metabolism and, ultimately, structure (Volpe, 1995). The acutely ill cardiac population may be exposed to various degrees of hypoxia and ischemia, frequently resulting in cerebral oxygen and blood flow alterations and physiologic instability prior to surgery. The extent and nature of these acute or ongoing (i.e. until the time of surgery) hemodynamic changes may be responsible for the clinical manifestations of acute CNS compromise.

5.3.2 MICROCEPHALY: Microcephaly is defined as an impairment of intrauterine brain growth and is characterized clinically as a head circumference of more than 2 standard deviations (SD) below the mean for gestational age (Ross & Frias, 1977; Volpe, 1995). The small size of the skull reflects a small brain, however it is not the size of the brain that is associated with the common manifestations of mental retardation, rather it is the underlying structural pathology of the brain. An abnormally small brain results either from anomalous development during the first seven months of gestation (i.e. primary microcephaly) or from an insult induced during the last 2 months of gestation or during the perinatal period (i.e. secondary microcephaly) (Menkes, 1995). Primary

microcephaly usually is the result of a variety of genetic or environmental insults that cause an anomaly of induction and migration. Numerous chromosomal disorders, such as trisomies, deletions, and translocations, are associated with primary microcephaly. In addition, dysmorphic syndromes with normal karyotypes as well as maternal exposure to ionizing radiation or infectious agents, notably cytomegalovirus, toxoplasma and rubella are also associated with microcephaly (Menkes, 1995). Secondary microcephaly may result from a variety of infectious, traumatic, metabolic, or anoxic insults, occurring during the last part of the third trimester, the perinatal period, or early infancy (Menkes, 1995).

Microcephaly reflects a pathological change in brain structure, usually occurring in fetal life, and neurodevelopmental outcome is very much dependent upon the extent and type of underlying pathology (Cowie, 1987). Both primary and secondary microcephaly display a broad spectrum of neurologic manifestations, ranging from decerebration, severe autistic behavior or mental retardation to a mild impairment of fine motor coordination. For example, Dolk and colleagues (1991) examined 41 infants born at term who maintained a head circumference less than or equal to 2 SD below the mean at a mean age of 7 years of age and found that 10.5% had an intelligence quotient (IQ) below 70, 28.1% had a borderline IQ (71-80), 43.0% had an IQ between 81-100 and only 14.0% had an IQ above 100 (IQ was not known in 4.4% of subjects). Similarly, Lipper et al. (1981) and Gross et al. (1978) concluded that head circumference at birth is a reliable predictor for future neurodevelopmental and intellectual outcome in a group of low birth weight infants.

In this study, more than one third (15/45) of newborns with CHD were microcephalic, suggesting the possibility of a congenital, intrauterine origin. The microcephaly in this cohort likely reflects a potential disruption in brain development before birth, during a period where the brain is normally undergoing the most rapid rate of cell division known as neuronal proliferation (Winick, 1973). Abnormal brain development may render the CNS vulnerable to a host of interferences with brain cell division that ultimately inhibit brain growth. Such alterations in cellular growth patterns may be clinically manifested and documented by head circumference measures during the first year of life (Winick & Ross, 1970). Moreover, 66.7% (10/15) of newborns with microcephaly in this sample also had abnormal neurologic examinations. This subgroup of children may therefore be at increased risk for later developmental disability, presumably due to congenital and acquired brain injury.

5.3.3 JITTERINESS: Jitteriness is a disorder of movement, that is generalized and symmetrical, and has the qualities of a 'coarse' tremor. It is stimulus-sensitive and can be diminished effectively by gentle, passive flexion of the limbs. Frequent accompaniments of jitteriness are brisk deep tendon reflexes and an easily elicited moro reflex. Jitteriness is most frequently related to insults that produce neuronal hyperirritability (e.g. hypoxic-ischemic encephalopathy, hypocalcemia, hypoglycemia and following withdrawal from sedation (e.g. fentanyl) (Volpe, 1995).

Four subjects presented with jitteriness of a coarse quality in our cohort, and all four had other abnormal neurologic findings including tone abnormalities

and poor state regulation. The jitteriness documented in these subjects may be one of the clinical manifestations of CNS 'irritability' given the acuity of illness in addition to marked and frequent hemodynamic alterations, resulting in CNS compromise. However, it should be noted that jitteriness is also noted in the context of normal neonatal neurobehavioral examinations (e.g. 18.7% of controls had course tremors), and therefore this finding should be integrated in the context of other neurologic abnormalities (e.g. tone abnormalities, poor state control, etc.) and not necessarily considered aberrant in isolation.

5.3.4 BEHAVIORAL STATE: State refers to the degree of consciousness or arousal. Neurobehavioral state organization is defined as an infant's ability to regulate and demonstrate well defined states, and make smooth and organized transitions between states (i.e. sleep to arousal, to alert, to crying). State organization is one indicator of central nervous system maturity and integrity. The infant who cannot be aroused, who is excessively irritable or who swings abruptly between sleep and crying states with no alert periods may be demonstrating CNS immaturity or a pathologic condition (Hunter, 1996). An infant's distribution of states, as well as the ability to make smooth transitions between states, is dependent on a number of variables. These include the age or maturity of the infant, neurologic integrity, the infant's general well-being, medication, pain or discomfort, physiologic variables such as hunger or at what point in the sleep-wake cycle an infant is in (Brazelton, 1995).

Als (1983) has provided a model for understanding the role of state and behavioral cues in determining the stability and organization of an infant. An

infant's response to the environment and the quality of its interactions can be manifested through behaviors in any one of four hierarchical systems: the autonomic or physiologic system, the motoric system, the state system or the attentional system. Optimal self-regulation occurs only when there is appropriate physiologic stability. Therefore, in order to achieve behavioral state regulation, the infant must first attain physiologic stability and homeostasis. For example, a full term baby displays clear differentiation as well as smooth transition between states. The baby with state stability and attentional regulation is described as having: clear sleep states, rhythmical, robust crying, effective self-quieting and consolability, and focused alertness and attention when awake. Premature infants frequently lack maturity and physiologic stability, and their states are disorganized and poorly differentiated.

Twenty five (60.9%) newborns with CHD demonstrated 'poorly modulated' behavioral state organization profiles when compared to behavioral-state repertoires described in healthy full term neonates. Als et al. (1979) proposed that poor behavioral state organization in preterm infants may serve as a necessary protective reflex for shutting out excessive stimulation in an attempt to maintain physiologic homeostasis. However, this may have a secondary consequence of sensory and interactional deprivation.

This hypothesis may also be applied to the acutely ill newborn with CHD who has come from a very stable intrauterine environment, to a relative unstable extrauterine environment given their cardiorespiratory compromise. Poor state regulation documented in more than half of subjects may serve as an intrinsic protective mechanism in an attempt to obliterate further physiologic instability

exacerbated by the extrinsic environment. Frequent autonomic fluctuations in heart rate, respiratory rate, and oxygen saturation may lead to CNS 'irritability' or 'overload' and consequently an intrinsic protective response may come into play in order to minimize any added stresses that challenge the intrinsic attempts at autonomic or physiologic equilibrium. Poor behavioral-state organization may have affected subject's neurobehavioral performance at the time of assessment. One could postulate that the poor state regulation may be evidence of acute hypoxic-ischemic injury.

5.3.5 FEEDING: Decreased endurance is a common feeding problem in infants with CHD often times as a result of tachypnea, and/or tachycardia, or congestive heart failure, and may result in insufficient oral intake (Barkin, 1986; Wolf & Glass, 1992). Since the baseline heart rate may be fast, the infant may have limited capacity to increase the heart rate to respond to the added energy demands of feeding (Pittman & Cohen, 1964). In addition, with decreased energy stores and decreased delivery of oxygen for work, the infant may have inadequate strength to produce an effective suck. Nutritive suck may be weak, sucking bursts may be short, with longer than average pauses taken to rest and recover. This results in an overall decrease in sucking time and subsequent oral intake (Wolf & Glass, 1992).

Failure to thrive is a frequent accompaniment of congenital heart defects (Lynch & Sweatt, 1987), whereupon infants appear to have a suboptimal intake, coupled with a lack of drive to eat. The presence of congestive heart failure can lead to delayed gastric emptying and gastrointestinal hypomotility, which may account for the poor appetite seen in a subgroup of infants. However,

inadequate intake may not be the sole reason for growth failure. The undernourished state may also be partly due to increased metabolic requirements (Pittman & Cohen, 1964). Oxygen consumption is higher in patients with congenital heart defects given increased metabolic demands from the muscles of respiration as well as the heart muscle (Vanderhoof et al., 1982). With increased metabolic needs, greater nutritional intake is required for optimal growth, and the volume required to obtain optimal growth may be above and beyond the baby's capacities. Finally, impaired CNS integrity may also be an important limitation of oral feedings (Davenport, 1988). Neurologic injury in the form of hypoxic-ischemic encephalopathy, cerebral embolisms, seizures, or tone abnormalities, may affect a child's oral-motor and feeding abilities. Moreover, developmental immaturity will influence the rate of acquisition of normal feeding skills or may affect the infant's persistence at feeding.

Eleven (26.8%) subjects demonstrated a weak non-nutritive suck, 3 had no suck and 15 (33.3%) presented with decreased feeding efficiency. Moreover, all newborns with a weak suck were also found to be hypotonic on neurobehavioral assessment. Therefore, poor oral-motor skills do not only appear to be exclusively the result of cardiorespiratory compromise, but possible CNS injury or transient perturbation may impact on feeding patterns.

5.4 Somatosensory evoked potential findings

Evoked potential recordings are widely used in the pediatric milieu to evaluate the maturity and intactness of ascending sensory pathways of the CNS. Evoked potentials are noninvasive, objective and reliable measures of CNS

function. These neurophysiologic techniques evaluate the functional integrity of the ascending neuraxis and therefore have diagnostic value for a wide spectrum of disorders (Chiappa, 1990; Gilmore, 1989; Laureau, 1988).

Evoked potential abnormalities are common in high-risk newborns, and these findings may reflect various types of brain injury or maldevelopment. The predictive value of SEP recordings has received much attention, given the close proximity of the generators of the parietal potential to the motor strip and to the periventricular region, regions that are vulnerable to hypoxic-ischemic exposure. Several investigators have examined the predictive value of SEP recordings in high-risk newborns, including premature and full term asphyxiated infants (Gibson et al., 1992; Gorke, 1986; Klimach et al., 1988; Laget et al., 1976; Luschg et al., 1983; Majnemer et al., 1988, 1990, 1996; Taylor et al., 1992; Willis et al., 1987, 1989). Overall, sensitivity, specificity, and predictive value typically range between 80-100%. Absent parietal potentials are a very poor prognostic sign, while increased central conduction time appears to be associated with mild to moderate developmental deficits (DeVries et al., 1991; Gibson et al., 1992; Majnemer et al., 1990, 1995, 1996; Pierrat et al., 1993; Taylor et al., 1992; White & Cooke, 1994).

SEP recordings were obtained in 33.3% of our cohort (n=15), as the remainder of the subjects were medically unstable, and therefore could not leave the unit. Of the 15 tested, 2 subjects had abnormal recordings consisting of bilateral absence of N19/P22 potentials, which is associated with poor prognosis in neonatal intensive care survivors. The remainder of subjects had normal SEP recordings, which may suggest that few will have severe sequelae, or perhaps the pattern of injury may be more mild and diffuse, or not affecting the structures and

pathways recorded by SEP. It should also be considered that subjects tested were determined to be medically stable, whereas those not tested were too unstable for transport to the laboratory. These findings may not be representative of the overall infant cardiac population, but rather a subgroup of stable babies that present to cardiology in the newborn period, prior to surgery. It would be of interest for future studies to use portable evoked potenital equipment so as to evaluate this cohort more comprehensively using electrophysiologic testing in order to have a representative sample of this population.

5.5 Performance on the ENNAS (subjects versus controls)

Early studies describing the neurologic examination of at risk newborns have delineated that abnormal signs such as hypoactive primitive reflexes, abnormal muscle tone and ocular signs, diminished or shill cry, and decreased arousal are associated with an increased risk for neuromotor deficits in childhood (Dargassies, 1971; Lott, 1989; Volpe, 1979). Moreover, standardized assessments of high-risk neonates distinguish abnormal signs when compared to healthy term newborns (Als et al., 1985; Costas et al., 1989; Emory et al., 1989; Piper et al., 1985). Neurobehavioral performance has been reported to be more abnormal ($p<.05$) among infants born small for gestational age (SGA) or asphyxiated at term (Costa et al., 1989; Majnemer et al., 1993; Piper et al., 1985). Emory et al. (1989) described poor orienting responses in high-risk infants with seizures when compared to newborns without seizures. Majnemer and colleagues (1993) demonstrated significant differences in overall test performance and individual items on the ENNAS in full term asphyxiated and SGA newborns as

compared to healthy term controls. Poor orienting responses, abnormal muscle tone, and weaker or diminished motor responses and reflexes were reported.

Comparison of performance on the ENNAS between subjects with CHD and healthy full term controls demonstrated significant differences in test performance between the two groups, particularly in the distribution of scores. Poor visual and auditory responses were characteristic of the vast majority of newborns with CHD, however performance may have been influenced by poor organization of state which was a hallmark feature in this cohort. In addition the distribution of passive and active movements was also very distinct between the two groups. Newborns with CHD manifested a) weak motor responses, such as neck extension in prone, antigravity movements during ventral suspension and head righting in supported sitting positions, b) decreased flexion in limb traction and recoil as well as c) limited spontaneous movements and d) muscle tone abnormalities. These differences in performance between the two groups may in part be reflective of acute cardiorespiratory compromise which may limit their motor activity and responsiveness to the external environment, in an attempt to best conserve energy needed to maintain physiologic stability. Nonetheless, deviant performance due to perinatal brain injury cannot be ruled out as a causal factor. Normal ENNAS is reassuring in half of our cohort, however the high prevalence of acute neurobehavioral abnormalities is worrisome. The literature suggests that many of these neonates may be at substantial risk for subsequent neurodevelopmental sequelae (Allen et al., 1989; Majnemer et al., 1994).

5.6 Relationship between neurobehavioral performance and cardio-respiratory status

The relationship between specific physiologic and medical factors and neurobehavioral performance was examined to determine if neurobehavioral status was reflective of and influenced by the acuity of illness. The overall prevalence of neurobehavioral abnormalities documented within the entire cohort was approximately 50%. Statistical analysis revealed no significant association between the medical and/or physiologic parameters examined (i.e. oxygen saturation, tachypnea, congestive heart failure, intubation, prostaglandins) and an increased risk for neurological findings with the exception of cyanotic versus acyanotic defects. An increased risk for neurobehavioral abnormalities was observed in those neonates with acyanotic defects. This may be attributed to irregular fluctuations in blood pressure and/or blood flow that is associated with acyanotic defects. Pump failure or pressure overload secondary to obstruction may lead to insufficient blood flow to the various organ systems, particularly the brain. Furthermore, injury may be the result of cumulative insults where large swings in blood pressures and subsequent alterations in cerebral perfusion occur, possibly resulting in impaired autoregulation (Volpe, 1995). Conversely, newborns with cyanotic CHD (defined as decreased oxygen in the blood) may demonstrate sufficient adaptability to chronic static hypoxemia. Metabolic needs may be reduced or redistributed to organ systems with the greatest oxygen requirements to accommodate for the oxygen insufficiency in the blood. These hypotheses (re: mechanisms of brain injury associated with acyanotic CHD) would need to be substantiated by future experimental studies.

5.7 Validity of findings

The value of the neonatal neurologic examination is in defining the locus and extent of neuropathological involvement, the diagnosis of acute neurologic injury and the identification of the 'high-risk' newborn. The neurologic examination is an adjunct to other modalities which include electroencephalography, evoked potentials and neuroimaging procedures, and are used collectively for diagnosis and prognostication (Volpe, 1995).

Occupational therapists carry out a complementary approach which evaluates the neurobehavioral status of newborns 'at-risk'. Neurobehavioral assessments provide the opportunity to evaluate the infants' abilities to regulate state and to make smooth transitions from sleep, alert and crying periods, which is one indicator of central nervous system maturation and integrity. These assessments also explicitly evaluate detail passive and active movements, primitive reflexes, and auditory and visual orienting responses (Hunter, 1996). The purpose of this evaluation is to identify and monitor the neurobehavioral performance of newborns at high risk for neurodevelopmental sequelae and therefore target those in need of early developmental intervention. In summary, the key role of the pediatric neurologist is to define the presence and location of central nervous system injury, whereas the occupational therapist's primary goal is the early identification of newborns at risk who are in need of prompt therapeutic interventions in order to minimize long-term disability. These two independent assessments performed by the neurologist and occupational therapist are considered to be complementary rather than substitutes for each other.

Although different approaches are employed by the occupational therapist and the neurologist in the neurologic assessment of high risk newborns, both are evaluating the maturity and integrity of the immature nervous system. The results of our study indicate that there is excellent agreement (kappa=0.94) between the neonatal neurobehavioral assessment and the standard neurological examination on the overall impression of the newborn. Within the cohort studied, approximately half were neurologically normal on examination, whereas half demonstrated specific neurologic abnormalities. It should be noted that the examiners agreed in their assessments of both normal and abnormal subjects, and strongly concurred on key elements of the evaluation (e.g. muscle tone, symmetry, abnormal movement patterns, non-nutritive suck). The neurologic examination encompasses components such as head circumference, cranial nerve function and state of consciousness, whereas the neurobehavioral assessment measures behavioral state organization, orienting responses and a complex repertoire of motor acquisitions in various positions. These latter items are unique contributors of each evaluation, emphasizing the complementary nature of these diagnostic tools.

The validity of neurologic observations in newborns is presently underappreciated in the clinical milieu. The results indicate that there is strong overall agreement (i.e. concurrent validity) between two neonatal neurologic assessment approaches, suggesting that the neonatal neurologic examination as presently constructed is indeed consistent and valid.

5.8 Clinical implications

The challenge confronting health care professionals caring for high-risk newborns in the neonatal intensive care unit is not only to ensure survival, but to minimize long-term morbidity. While prevention is the ultimate goal, early identification of high-risk neonates is paramount, so that remediation may be initiated without delay, in order to minimize future neurodevelopmental morbidity and ultimately maximize functional potential. Several studies have examined the predictive value of neonatal neurobehavioral examinations in newborns at risk for neurodevelopmental sequelae. The neonatal neurologic examination has a very good negative predictive value and sensitivity for psychomotor function in children, however the predictive validity of neonatal neurobehavioral assessments in newborns is limited by a high rate of false positive findings (Allen & Capute, 1989; Dubowitz et al., 1984; Haddars-Algra et al., 1986; Nelson & Ellenberg, 1979; Majnemer et al., 1994, 1995). Studies however, have predominantly focused on neurologic outcome, with very few studies employing formal or standardized developmental assessments as outcome measures. Populations of interest have primarily consisted of infants who have been exposed to prenatal or perinatal hypoxic-ischemic injury, who are at enhanced risk for developmental handicap. Research to date suggests that neonatal neurobehavioral examination may be more valuable at predicting more complex skill acquisition, particularly in the language and cognitive domains. Therefore, initial false-positive findings documented on follow-up (e.g. at 1 year of age) become true positives later on (e.g. 3 and 5 years of age) (Hack et al., 1994; Majnemer et al., 1995; McCormick et al., 1992; Robertson et al., 1992; Saigal et al., 1991,1994).

Our results show that neurobehavioral abnormalities were present in more then half of the neonates with CHD examined. The results suggest that this population may be at increased risk for long-term neurodevelopmental disabilities, therefore newborn screening may be warranted, in an attempt to identify as well as target those infants 'at-risk' for developmental handicap. Long term follow-up of this cohort is needed to determine if abnormalities detected acutely are transient, or are markers for future developmental disability.

5.9 Limitations

Subjects were consecutively recruited once their diagnosis was confirmed by the cardiologist. However, subjects that were medically unstable necessitating immediate surgical intervention were missed. Clinical assessment of the very ill neonates was at times limited and incomplete owing to the presence of central or peripheral lines, ventilators, etc., therefore restricting the amount of handling and position change. As a result, the prevalence of neurobehavioral abnormalities may be underestimated. SEP were performed in a small portion of subjects given that those subjects that were medically unstable were not transported to the clinical neurophysiology laboratory, thus generalization of findings is limited. Finally, cardiorespiratory status was documented at the time of neurobehavioral assessment, when subjects were generally stable from a cardiorespiratory standpoint. This may not however, reflect the acuity of illness that may be present on admission. Although neurobehavioral abnormalities were common, the long-term implications with regards to developmental outcome are unknown. Longitudinal follow-up of our cohort is now underway so that we may

ascertain whether these abnormalities are transient or have long-term significance.

5.10 Future directions

In the context of this ongoing prospective study, we will examine the cardiorespiratory status of newborns with CHD on admission using the Score of Neonatal Acute Physiology (Richardson et al., 1993), to determine if perinatal cardiorespiratory compromise at the time of admission is correlated with neurobehavioral abnormalities. Newborns that are medically unstable at the time of admission may be at increased risk for brain injury, as compared to neonates that are stabilized medically. In addition, long-term follow-up studies are presently underway to determine the predictive value of these acute neurobehavioral findings. We are presently continuing to recruit subjects and with the increased sample size we hope to carry out multiple regression analysis to evaluate the relationship between neurologic status and a set of cardiorespiratory variables including the type of congenital heart defect.

5.11 Significance

As mortality rates for open heart surgery in early infancy continue to decline dramatically, the neurodevelopmental outcome of survivors has come under increasing scrutiny. Our findings suggest that the prevalence of neurobehavioral abnormalities in the infant cardiac population prior to open heart surgery has been underappreciated and that these infants may warrant regular developmental screening. Furthermore, the relatively high occurrence of neurobehavioral

abnormalities may be evidence of brain injury due to cardiorespiratory compromise or congenital malformation prior to surgery, with long-term neurodevelopmental consequences. Moreover, preoperative neurologic dysfunction may in turn, render infants more susceptible to further neurological injury during cardiac surgery and hence may impact on their long term outcome. Survival as a goal has been largely achieved. Future studies are needed to assess the prevalence and determinants of brain injury, so that neurologic sequelae of congenital heart disease may be reduced. Given the multiple needs of this infant cardiac population, interdisciplinary efforts between cardiac surgeons, cardiologists, intensive care unit personnel, pediatric neurologists, developmental specialists as well as clinical nutrition experts is critical in order to best meet the needs of this group of high-risk newborns. Such collaborative efforts are essential to prevent and/or minimize neurodevelopmental morbidity through early identification of infants 'at-risk', and initiation of early intervention programs in order to enhance the quality of life of these young survivors of CHD.

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APPENDIX A

OCCUPATIONAL THERAPY FORM

Subject Identification Sheet

Name of subject: _____

Date of birth: _____

Gestational Age: _____

Birth weight/percentile: _____

APGAR: _____

Gender: _____

Diagnosis: _____

Secondary Diagnos(es): _____

_____

OCCUPATIONAL THERAPY FORM

Observation Sheet

Evaluation: _____ 1. neonatal

_____ 2. pre-operative

_____ 3. post-operative

_____ 4. 1 year post-operative

1. Name of subject _____

2. Date of assessment _____

3. Age at assessment _____

Feeding

4. Feeding method: _____ 1. PO

_____ 2. supplementation (NG)

_____ 3. NPO (IV) or TPN

5. Feeding efficiency: ____ 1. normal

_____ 2. decreased

6. Other feeding abnormalities:

Behavior/Activity Level

7. Agitated: ____ no ____ yes

8. Restlessness: ____ no ____ yes

9. Irritable: ____ no ____ yes

10. Lethargy: ____ no ____ yes

11. Activity: ____ 1. normal ____ 2. poor state reg. ____ 3.decreased

12. Tone:

____ 0. hypotonic

____ 1. slightly floppy

____ 2. normal

____ 3. slightly hypertonic

____ 4. moderately hypertonic

____ 5. opisthotonic (sustained extensor posture of head and trunk)

____ 6. mixed tonicity across head, trunk, upper and lower extremities

13. Abnormal Movement Patterns:

____ 1. normal

____ 2. jitteriness/ tremor

____ 3. other

Impression: ____ 1. normal

____ 2 abnormal

APPENDIX B

Neurologic Examination

NAME OF PATIENT: _____
DATE OF BIRTH: _____
DATE OF ASSESSMENT: _____
EXAMINER: _____

Overall Neurologic Exam Score:

__1. normal
__2. abnormal

Head Circumferance: _____cm. Percentile: _____

Muscle Tone:
__ 1. hypotonic)little or no resistance to manipulation)
__ 2. slightly floppy
__ 3. normal
__ 4. slightly hypertonic
__ 5. moderately hypertonic (exaggerated resistance to extension of extremities, tendency for head extension to predominate)
__ 6. opisthotonic (sustained extensor posture of head and trunk)
__ 7. mixed tonicity across head, trunk, upper and lower extremities

Muscle Tone:
asymmetry __ yes; greater on the __ right, __ left.
__ no

distribution __ 1. spastic quadriplegia
__ 2. spastic diplegia
__ 3. spastic hemiplegia
__ 4. spastic monoplegia
__ 5. choreoathetosis
__ 6. dystonia
__ 7. other: _____

Muscle Bulk: Upper extremities __ 1. normal
__ 2. abnormal: _____

Lower extremities __ 1. normal
__ 2. abnormal: _____

Muscle Power:Upper extremities __ 1. normal
__ 2. abnormal: _____

Lower extremities __ 1. normal
__ 2. abnormal: _____

Deep Tendon Reflexes: UE: left / right LE: left / right
__ __ __ __

(1= normal, 2= decreased, 3= increased)

Cranial Nerves: __ 1. all appear intact
__ 2. 1 or more abnormalities
comments: _____

Motor Development: gross motor: __ 1. normal
__ 2. delayed
comments: _____

fine motor: __ 1. normal
__ 2. delayed
comments: _____

Quality of Movements:

check off any movement abnormalities noted on examination:

movement disorder	upper extremity		lower extemity		oral-motor	other
	left	right	left	right		
1. athetosis						
2. chorea						
3. dystonia						
4. tremor						
5.myoclonus						
6. ataxia						
7. other						

APPENDIX C

SOMATOSENSORY EVOKED POTENTIALS

Data Sheet

Name of patient: _____

Date of birth: _____

Date of Assessment: _____

Gestational Age: _____

Age at Assessment: _____

Assessment: _____ 1. Neonatal

_____ 2. Pre-operative

_____ 3. Post-operative

Latency	Left median nerve		Right median nerve	
	value	score	value	score
E.P.				
CII				
C'c				
N13-N19				

Score: 1=normal 2=abnormal

N19/P22 waveform configuration _____ Left _____ Right
(1=normal, 2=low amplitude + dispersed for age, 3=absent)

Overall score:

_____ 1. Normal

_____ 2. Increased latencies (unilaterally/bilaterally)

_____ 3. Absent N19/P22

APPENDIX D

CARDIO - RESPIRATORY STATUS

Name of Subject: _____

MCH #: _____

Weight: _____

Diagnosis: _____

____ Cyanotic _____ Acyanotic

Date of Assessment: _____

Feeding: ___ 1. NPO

____ 2. 100 %

Respiratory Rate: ____1. normal Heart Rate:

____ 2. tachypnea (> or = 55)

____ 3. IMV (respirator)

Oxygen Saturation: _____

CHF: ____ 1. no

____ 2. yes

Treatment: ____ 1. PGE ____ 4. antibiotics

____ 2. Lasix ____ 5. anticonvulsives

____ 3. digoxin _____6. other

Overall rating: _____

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APPENDIX E

NEUROBEHAVIORAL STATUS OF NEWBORNS WITH CONGENITAL HEART DEFECTS

This is a research study being performed by Catherine Limperopoulos, O.T. (C), under the supervision of Dr. A. Majnemer (School of Physical & Occupational Therapy, McGill University), in collaboration with Dr. Rosenblatt (Neurology), Dr. Rohlicek (Cardiology) and Dr. Tchervenkov (Cardiovascular surgery).

The aim of this study is to evaluate the early developmental patters of newborns with congenital heart defects. Infants with difficulties in breathing and with blood circulation early in life may exhibit poor responsiveness to their environment. We would therefore like to verify that your child's developmental patterns are appropriate. The information obtained from this study may help to minimize any identified developmental problems in this population using early therapeutic intervention.

The study will involve an assessment in the newborn period which will be carried out by an occupational therapist once your child is medically stable. The assessment involves examination of your baby's movements in different positions, and his/her response to visual and auditory stimuli (e.g. response to rattles, faces). The assessment takes approximately 20-30 minutes to administer. A pediatric neurologist will briefly examine your child's reflexes, muscle tone and movement patterns (about 15 minutes). As well, somatosensory evoked potentials will be performed to assess the maturity of the nervous system. For this test, recording devices are pasted with a cream on the neck and scalp, and a sensory stimulator is placed on the wrist, similar to those used for an E.K.G. (which monitors your child's heart beat). This test, which takes about 30 minutes to complete, looks at how information is transmitted from a nerve in the hand to the brain. This test is in no way harmful or painful to the child. No needles or radiation are used.

All personal data will be kept confidential. Although there are no direct benefits in participating in this study, any pertinent findings will be communicated to your child's cardiologist. Participation in this research project is strictly voluntary. You may withdraw from the study at any time without affecting the quality of your child's care.

Thanking your for your cooperation. If you have any questions, please feel free to contact Catherine Limperopoulos, 934-4400, ext. 2110 or Dr. Majnemer, 934-4400, ext. 2902.

I have been informed of the procedures to be used and I understand them. I consent to the participation of my child _____ in this research study. I also understand that participation will not interfere in any with my child's ongoing care and that I am free to withdraw from the study at any time without prejudice.

Signature of parent/guardian _____

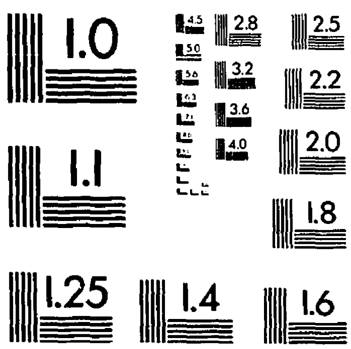
Witness _____

Date _____

Signature of principal investigator _____

Date _____

IMAGE EVALUATION
TEST TARGET (QA-3)



150mm

6"

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