Clinical report

Bilateral Striatal Necrosis in Two Subjects with Aicardi-Goutières Syndrome due to Mutations in *ADAR1* (*AGS6*).

Roberta La Piana[1], Carla Uggetti[2], Ivana Olivieri[3], Davide Tonduti[4], Umberto Balottin[3,4], Elisa Fazzi[5], Simona Orcesi[3].

Author Affiliations

1: Department of Neuroradiology, Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, Canada

2: Unit of Neuroradiology, Department of Radiology, San Carlo Borromeo Hospital, Milano, Italy

3: Child Neurology and Psychiatry Unit, C. Mondino National Neurological Institute, Pavia, Italy

4: Department of Brain and Behavioural Sciences, Unit of Child Neurology and Psychiatry, University of Pavia, Italy

5: Department of Clinical and Experimental Sciences, University of Brescia, Italy

Running title

Striatal necrosis in AGS due to *ADAR1* mutation.

Corresponding Author

Simona Orcesi, MD

Child Neurology and Psychiatry Unit, C. Mondino National Neurological Institute

via Ferrata 2, 27100 Pavia, Italy.

phone + 39 0382 380427-280; fax +39 0382 380289

e-mail: simona.orcesi@mondino.it

Word Count: 1930

ABSTRACT

Aicardi-Goutières syndrome (AGS) is a genetic inflammatory disease. The classic neuroradiological picture mimics that of congenital infections in that Aicardi-Goutières syndrome is characterized by leukoencephalopathy, brain atrophy and intracranial calcifications. To date, bilateral striatal necrosis has not been reported in patients with AGS.

We report two patients with clinical diagnosis of Aicardi-Goutières syndrome in which brain MRI and CT scans demonstrated bilateral striatal necrosis. The diagnosis of Aicardi-Goutières syndrome in these two patients was genetically confirmed after the recent discovery that mutations in the *ADAR1* (*AGS6)* gene may cause Aicardi-Goutières syndrome.

This is the first report of bilateral striatal necrosis in association with Aicardi-Goutières syndrome. These results expand the neuroradiological phenotype of Aicardi-Goutières syndrome.

Key words

Aicardi-Goutieres syndrome; *ADAR1*; infantile bilateral striatal necrosis.

INTRODUCTION

Aicardi-Goutières syndrome (AGS) (OMIM 225750) is a genetic inflammatory disease due to mutations in any one of six genes discovered to date (*AGS1-AGS6*). These genes are all involved in nucleic acid metabolism that can result in intracellular overload of nucleic acids activating TLR-IFN-alpha pathways.[Crow et al. 2006a; Crow et al. 2006b; Pulliero et al. 2011; Rice et al. 2009; Rice et al. 2012] In particular, the most recently described gene, *ADAR1* (*AGS6),* is involved in the suppression of type I interferon (IFN) signalling.[Riceet al. 2012]

The diagnosis of AGS is suspected when a child presents in the first year of life with acquired microcephaly, irritability, psychomotor delay or regression, unexplained fevers, and laboratory tests showing raised CSF IFN-α levels, lymphocytosis, and negative TORCH serology. Neuroradiological criteria - leukodystrophy, brain calcifications, and cerebral atrophy - have been crucial for the diagnosis of AGS since its very first description.[Aicardi and Goutieres 1984; Lebon et al. 1988] Although some recurring patterns seem to characterize the neuroradiological picture, significant variability in the above-mentioned criteria has been observed.[Uggetti et al. 2009] For example, a fronto-temporal gradient often associated with cystic degeneration is considered the classical pattern of leukoencephalopathy in AGS.[Uggettiet al. 2009] However, cases with more diffuse white matter involvement have also been described.[Rice et al. 2007; Uggettiet al. 2009] Brain calcifications in AGS are usually, but not always, bilateral and symmetric, and can be either punctate or gross, and either sparse or widely diffuse. Heterogeneity in localisation is also evident: calcifications can be present in the basal ganglia, dentate nuclei and/or in the white matter.[Uggettiet al. 2009] This heterogeneity is also seen in congenital infections whose phenotypes are mimicked by AGS.

As opposed to what observed in AGS, infantile bilateral striatal necrosis (IBSN) is a unique and very distinctive neuroradiological phenotype.[Goutieres and Aicardi 1982] IBSN is characterized by a specific involvement of the striata, with initial swelling of the putamina and caudates followed by degeneration, leading ultimately to cellular necrosis.[Goutieres and Aicardi 1982; Mito et al. 1986] IBSN has been associated with different genetic conditions, including mitochondrial disorders.[Aniello et al. 2008; Barel et al. 2008; Basel-Vanagaite et al. 2006; Dale and Brilot 2012; Lal et al. 2013] To date, IBSN

has not been associated to AGS. The aim of our study is to describe two patients with clinical diagnosis of Aicardi-Goutières syndrome and neuroradiological findings compatible with bilateral striatal necrosis.

CLINICAL REPORTS

Patient 1

An eight month-old male child, born at term after an uneventful pregnancy to healthy unrelated mixed Italian-Cuban parents, presented with extreme irritability and unexplained episodes of fever. The perinatal period was uneventful and the parents reported normal psychomotor development.

At the age of eight months, progressive psychomotor regression and generalized involuntary movements were evident. When referred to our clinic at the age of nine months, the neurological examination was characterized by bradykinesia, rigidity, spasticity and microcephaly. The head CT scan demonstrated bilateral and symmetric calcifications at the level of the posterior aspect of the putamina (Figure 1A). The brain MRI (Figure 1D-E) showed diffuse white matter abnormalities compatible with leukodystrophy. Highly abnormal hyperintense signal - inhomogeneous in T2-weighted images (partly due to calcifications) and more homogeneous in T1-weighted images - was visible in both putamina, mainly in their posterior aspect. The T2-hyperintense signal was also observed in the body of the caudate nuclei bilaterally, with relative sparing of the heads, and, to a lesser extent, in the pallida nuclei (Figure 1D)

The follow up MRI examination performed three months later (Figure 1F) showed that the T2 hyperintense signal at the level of the putamina was more prominent. A marked atrophy of both putamina and caudate nuclei was observed. Consequently, the lateral ventricles appeared significantly enlarged. The white matter abnormalities were unchanged. No MR spectroscopy was performed.

Extensive laboratory and metabolic tests (including serology for TORCH, HIV-1 and -2, serum α-IFN, CSF lactate and pyruvate, and CSF lymphocyte count) were all normal, except for raised CSF alpha-IFN (12 UI/l; normal values <2). Reduction in the activity of the respiratory chain complexes (residual activity ranging from 45 to 63%, except for 27% for complex III) was documented on muscle homogenate. Southern Blot hybridisation, real-time PCR, and molecular analysis of *UQCRB*, *UQCRQ*, and *BCS1L* were normal.

The identification of two mutations in *ADAR1* (p.Pro193Ala (c.577C>G) and p.Lys359Argfs*14 (c.1076_1080del) on exon 2) established the diagnosis of AGS.

Patient 2

The second patient was a male infant born at 36th week of gestation after an uneventful pregnancy from non-consanguineous Italian parents. Birth weight and head circumference were in the 50-75th percentiles. At the age of one month, he presented with increasing irritability, as well as sleep and feeding difficulties. No recurrent fevers were reported. In the following months, psychomotor delay was noticed, as head control was never achieved. At the age of eight months, a thorough clinical and diagnostic workup was performed. The head CT scan revealed bilateral calcifications at the level of the putamina (Figure 1B) and enlarged ventricles, probably secondary to white matter atrophy. AGS was suspected based on the clinical and CT findings; however, the CSF analysis showed no lymphocytosis and mild elevation of alpha-interferon (3UI/ml; normal values <2). The CSF lactate was also moderately elevated (5.4mg%; normal values <3.5). The activity of the respiratory chain complexes was not measured for the patient. Blood tests for the TORCH complex were negative.

At the age of three years, the brain MRI demonstrated diffuse white matter abnormalities suggestive of leukodystrophy, loss of posterior periventricular white matter, and mild cerebral atrophy (Figure 1C). Abnormal T2-hyperintense signal was evident at the level of the putamina. Severe atrophy of the putamina and caudate nuclei with consequent enlargement of the lateral ventricles was also observed.

Another brain CT scan was performed at the age of 10 years and confirmed the presence of punctate bilateral and symmetric calcifications localized exclusively at the level of the putamina, mainly in their lateral aspect. In comparison to the previous exam, the calcium deposits appeared less prominent. The identification of mutations in *ADAR1* (p.Pro193Ala (c.577C>G) on exon 2 and p.Ala870Thr (c.2608G>A) on exon 8) confirmed the clinical diagnosis of AGS.

DISCUSSION

We observed two patients for which the diagnosis of AGS was first clinically suspected, and then genetically confirmed based on mutations in *ADAR1*, despite neuroradiological findings not reported before in large series of AGS cases.[Crowet al. 2006b; Uggettiet al. 2009] In particular, the leukodystrophy and cerebral atrophy were not as remarkable as commonly observed, while the bilateral involvement of the putamina – and in Patient 1 the caudate as well - was present since the disease onset in the first year of life. The striatal involvement was characterized by signal alteration, volume loss, and

calcification. In Patient 1 we could observe the evolution from the subacute phase and, hence, document the initial swelling of the striata nuclei. These neuroradiological findings (and, in Patient 1, their evolution over time) are fully compatible with bilateral striatal necrosis. Noticeably, we observed bilateral calcifications in the putamina. While this feature is not always present in IBSN, brain calcifications in AGS are seldom limited to a single structure.[Uggettiet al. 2009] Although we cannot exclude absolutely that IBSN and AGS represent a casual association, it is possible that the two subjects here reported represent a new distinct pattern of disease sharing the same imaging and genetic features.

IBSN was originally classified into two distinct entities.[Dale et al. 2002; Goutieres and Aicardi 1982] In the first subgroup, patients present subacutely in the first year of life, no relation with infections is found, and the pathogenesis is thought to be metabolic/heredodegenerative. Mitochondrial disorders – and among these complex III deficiencies[Barelet al. 2008] – may present with IBSN.[Anielloet al. 2008; Basel-Vanagaiteet al. 2006; Dale and Brilot 2012] In the second subgroup, the disease onset is more acute and clinical or serological evidence of an infectious process that preceded the neurological symptoms is commonly documented.[Goutieres and Aicardi 1982] Both AGS patients reported here presented features overlapping the two subgroups. Consistent with the second subgroup of IBSN, we observed an acute disease onset. However, no evidence of infection was found and the disease course appeared to be progressive, suggestive of the first subgroup of IBSN. Moreover, no familiarity for similar neurological conditions was reported.

Interestingly, the pathogenesis of AGS is both immune-mediated and inflammatory. Similarly, IBSN has been associated with either immune-mediated reactions triggered by the interaction between self-antigens selectively present in the striata and exogenous agents.[Daleet al. 2002; Goutieres and Aicardi 1982] Among these agents, several viruses[Cambonie et al. 2000; Goutieres and Aicardi 1982; Murakami et al. 2005; Voudris et al. 2002; Yamamoto et al. 1997] were reported and notably AGS is described as mimicking viral infections. As reported by Rice et al., *ADAR1*-deficient cells may lead to an increase in immunoreactive dsRNA with consequently impaired suppression of IFN induction.[Riceet al. 2012] We hypothesize that the putamina and caudate nuclei of children with *ADAR1* mutations have a selective vulnerability, perhaps caused by the presence of self-antigens, that ultimately leads to IBSN. Moreover, metabolic changes occurring in the developing basal ganglia at disease onset may play a role

in the final clinical and neuroradiological picture.[Mitoet al. 1986] Interestingly, the striatum is particularly susceptible to neurotoxicity associated with HIV infection [Nath et al. 2000] and the metabolism of retroelements is central in the pathogenesis of both AGS and HIV.[Riceet al. 2012]

A mitochondrial dysfunction – in particular, a marked reduction of complex III activity - was documented in Patient 1. Previous reports of genetically-confirmed AGS patients have also noted mitochondrial respiratory chain deficiencies or mitochondrial involvement.[Barnérias et al. 2006; Leshinsky-Silver et al. 2011] In these reports, mitochondrial dysfunction was hypothesized to be secondary to the pathogenetic process of AGS. We speculate that in our patients, at least in Patient 1, the mitochondrial dysfunction could contribute to IBSN.

The diagnosis of AGS has always been based upon clinical and neuroradiological criteria, and then genetically confirmed.[Riceet al. 2007] Regarding the most classical laboratory diagnostic criteria for AGS, we observed normal CSF lymphocytes count, yet elevated CSF alpha interferon in both our patients. Although these features have already been described [Crow and Livingston 2008; Riceet al. 2007], we cannot exclude that this discordance between elevation of white cells and alpha interferon could be characteristic of *AGS6* patients [Riceet al. 2012]. Our report demonstrates that the classical neuroradiological criteria are not sufficient to describe the complex spectrum of AGS. However, we believe that some similarities are shared. In fact, both the classical neuroradiological picture and the one here reported resemble viral or immune-mediated disease. In addition, it is well known that genes involved in AGS are all related to metabolism of retroelements that, when not functioning, give rise to immune reactions similar to those triggered in response to viral stimulation.[Crowet al. 2006a; Crowet al. 2006b; Riceet al. 2009; Riceet al. 2012] In this regard, the neuroradiological picture observed in our two AGS patients with IBSN is in keeping with the notion that AGS mimics viral/immune-mediated processes due to an aberrant immune response consequent to impaired metabolism of nucleic acids. Finally, as mentioned above, the mitochondrial dysfunction documented in one case could have contributed to IBSN. A limitation of our study is that the findings we reported were observed in only two patients. Therefore, the hypotheses regarding the association between the two conditions (AGS and IBSN) and their pathogenesis need to be confirmed with further observations. Nevertheless, we can speculate whether other cases of IBSN of unexplained origin (i.e. no evidence of previous infection) could represent

undiagnosed cases of AGS and consequently whether the analysis of *ADAR1* should be suggested in those circumstances.

ACKNOWLEDGEMENTS

The Authors would like to thank Dr. Yanick J Crow for performing the genetic analyses and for his guidance and leadership in efforts towards learning about AGS, Dr. Gillian I. Rice for performing genetic analysis, Dr. S. Bastianello, Dr. E. Bertini and Dr. M.L. Carpanelli for providing neuroradiological and clinical data of the patients, Dr. G. Comi for performing mitochondrial respiratory chain and mitochondrial genetic analysis, Dr. D. Tampieri for providing technical support. Special thanks go to the International Aicardi-Goutières syndrome association (IAGSA) and to the affected children and their families for their support and encouragement in our work. This research has received funding from the European Union's Seventh Framework Program (FP7/2007-2013) under grant agreement number 241779. Roberta La Piana has received the Preston-Robb fellowship grant from the Montreal Neurological Institute. The authors have no competing interest to declare.

References

Aicardi J, Goutieres F. 1984. A progressive familial encephalopathy in infancy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis. Ann Neurol 15(1):49-54.

Aniello MS, Martino D, Petruzzella V, Eleopra R, Mancuso M, Dell'Aglio R, Cavallo M, Siciliano G, Defazio G. 2008. Bilateral striatal necrosis, dystonia and multiple mitochondrial DNA deletions: Case study and effect of deep brain stimulation. Movement Disorders 23(1):114-118.

Barel O, Shorer Z, Flusser H, Ofir R, Narkis G, Finer G, Shalev H, Nasasra A, Saada A, Birk OS. 2008. Mitochondrial Complex III Deficiency Associated with a Homozygous Mutation in UQCRQ. The American Journal of Human Genetics 82(5):1211-1216.

Barnérias C, Giurgea I, Hertz-Pannier L, Bahi-Buisson N, Boddaert N, PhD, Rustin P, Rotig A, Desguerre I, Munnich A, de Lonlay P. 2006. Respiratory chain deficiency in a female with Aicardi-Goutières syndrome. Developmental Medicine & Child Neurology 48(3):227-230.

Basel-Vanagaite L, Muncher L, Straussberg R, Pasmanik-Chor M, Yahav M, Rainshtein L, Walsh CA, Magal N, Taub E, Drasinover V, Shalev H, Attia R, Rechavi G, Simon AJ, Shohat M. 2006. Mutated nup62 causes autosomal recessive infantile bilateral striatal necrosis. Annals of Neurology 60(2):214-222.

Cambonie G, Houdon L, Rivier F, Bongrand AF, Echenne B. 2000. Infantile bilateral striatal necrosis following measles. Brain Dev 22(4):221-223.

Crow YJ, Hayward BE, Parmar R, Robins P, Leitch A, Ali M, Black DN, van Bokhoven H, Brunner HG, Hamel BC, Corry PC, Cowan FM, Frints SG, Klepper J, Livingston JH, Lynch SA, Massey RF, Meritet JF, Michaud JL, Ponsot G, Voit T, Lebon P, Bonthron DT, Jackson AP, Barnes DE, Lindahl T. 2006a. Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 cause Aicardi-Goutieres syndrome at the AGS1 locus. Nat Genet 38(8):917-920.

Crow YJ, Leitch A, Hayward BE, Garner A, Parmar R, Griffith E, Ali M, Semple C, Aicardi J, Babul-Hirji R, Baumann C, Baxter P, Bertini E, Chandler KE, Chitayat D, Cau D, Dery C, Fazzi E, Goizet C, King MD, Klepper J, Lacombe D, Lanzi G, Lyall H, Martinez-Frias ML, Mathieu M, McKeown C, Monier A, Oade Y, Quarrell OW, Rittey CD, Rogers RC, Sanchis A, Stephenson JB, Tacke U, Till M, Tolmie JL, Tomlin P, Voit T, Weschke B, Woods CG, Lebon P, Bonthron DT, Ponting CP, Jackson AP. 2006b. Mutations in

genes encoding ribonuclease H2 subunits cause Aicardi-Goutieres syndrome and mimic congenital viral brain infection. Nat Genet 38(8):910-916.

Crow YJ, Livingston JH. 2008. Aicardi-Goutieres syndrome: an important Mendelian mimic of congenital infection. Dev Med Child Neurol 50(6):410-416.

Dale RC, Brilot F. 2012. Autoimmune Basal Ganglia Disorders. Journal of Child Neurology 27(11):1470-1481.

Dale RC, Church AJ, Benton S, Surtees RA, Lees A, Thompson EJ, Giovannoni G, Neville BG. 2002. Post-streptococcal autoimmune dystonia with isolated bilateral striatal necrosis. Dev Med Child Neurol 44(7):485-489.

Goutieres F, Aicardi J. 1982. Acute neurological dysfunction associated with destructive lesions of the basal ganglia in children. Ann Neurol 12(4):328-332.

Lal D, Becker K, Motameny S, Altmüller J, Thiele H, Nürnberg P, Ahting U, Rolinski B, Neubauer B, Hahn A. 2013. Homozygous missense mutation of NDUFV1 as the cause of infantile bilateral striatal necrosis. Neurogenetics 14(1):85-87.

Lebon P, Badoual J, Ponsot G, Goutieres F, Hemeury-Cukier F, Aicardi J. 1988. Intrathecal synthesis of interferon-alpha in infants with progressive familial encephalopathy. J Neurol Sci 84(2-3):201-208.

Leshinsky-Silver E, Malinger G, Ben-Sira L, Kidron D, Cohen S, Inbar S, Bezaleli T, Levine A, Vinkler C, Lev D, Lerman-Sagie T. 2011. A large homozygous deletion in the SAMHD1 gene causes atypical Aicardi-Goutieres syndrome associated with mtDNA deletions. Eur J Hum Genet 19(3):287-292.

Mito T, Tanaka T, Becker LE, Takashima S, Tanaka J. 1986. Infantile bilateral striatal necrosis. Clinicopathological classification. Arch Neurol 43(7):677-680.

Murakami A, Morimoto M, Adachi S, Ishimaru Y, Sugimoto T. 2005. Infantile bilateral striatal necrosis associated with human herpes virus-6 (HHV-6) infection. Brain Dev 27(7):527-530.

Nath A, Anderson C, Jones M, Maragos W, Booze R, Mactutus C, Bell J, Hauser KF, Mattson M. 2000. Neurotoxicity and dysfunction of dopaminergic systems associated with AIDS dementia. J Psychopharmacol 14(3):222-227.

Pulliero A, Fazzi E, Cartiglia C, Orcesi S, Balottin U, Uggetti C, La Piana R, Olivieri I, Galli J, Izzotti A. 2011. The Aicardi-Goutieres syndrome. Molecular and clinical features of RNAse deficiency and microRNA overload. Mutat Res 717(1-2):99-108.

Rice G, Patrick T, Parmar R, Taylor CF, Aeby A, Aicardi J, Artuch R, Montalto SA, Bacino CA, Barroso B, Baxter P, Benko WS, Bergmann C, Bertini E, Biancheri R, Blair EM, Blau N, Bonthron DT, Briggs T, Brueton LA, Brunner HG, Burke CJ, Carr IM, Carvalho DR, Chandler KE, Christen HJ, Corry PC, Cowan FM, Cox H, D'Arrigo S, Dean J, De Laet C, De Praeter C, Dery C, Ferrie CD, Flintoff K, Frints SG, Garcia-Cazorla A, Gener B, Goizet C, Goutieres F, Green AJ, Guet A, Hamel BC, Hayward BE, Heiberg A, Hennekam RC, Husson M, Jackson AP, Jayatunga R, Jiang YH, Kant SG, Kao A, King MD, Kingston HM, Klepper J, van der Knaap MS, Kornberg AJ, Kotzot D, Kratzer W, Lacombe D, Lagae L, Landrieu PG, Lanzi G, Leitch A, Lim MJ, Livingston JH, Lourenco CM, Lyall EG, Lynch SA, Lyons MJ, Marom D, McClure JP, McWilliam R, Melancon SB, Mewasingh LD, Moutard ML, Nischal KK, Ostergaard JR, Prendiville J, Rasmussen M, Rogers RC, Roland D, Rosser EM, Rostasy K, Roubertie A, Sanchis A, Schiffmann R, Scholl-Burgi S, Seal S, Shalev SA, Corcoles CS, Sinha GP, Soler D, Spiegel R, Stephenson JB, Tacke U, Tan TY, Till M, Tolmie JL, Tomlin P, Vagnarelli F, Valente EM, Van Coster RN, Van der Aa N, Vanderver A, Vles JS, Voit T, Wassmer E, Weschke B, Whiteford ML, Willemsen MA, Zankl A, Zuberi SM, Orcesi S, Fazzi E, Lebon P, Crow YJ. 2007. Clinical and molecular phenotype of Aicardi-Goutieres syndrome. Am J Hum Genet 81(4):713-725.

Rice GI, Bond J, Asipu A, Brunette RL, Manfield IW, Carr IM, Fuller JC, Jackson RM, Lamb T, Briggs TA, Ali M, Gornall H, Couthard LR, Aeby A, Attard-Montalto SP, Bertini E, Bodemer C, Brockmann K, Brueton LA, Corry PC, Desguerre I, Fazzi E, Cazorla AG, Gener B, Hamel BC, Heiberg A, Hunter M, van der Knaap MS, Kumar R, Lagae L, Landrieu PG, Lourenco CM, Marom D, McDermott MF, van der Merwe W, Orcesi S, Prendiville JS, Rasmussen M, Shalev SA, Soler DM, Shinawi M, Spiegel R, Tan TY, Vanderver A, Wakeling EL, Wassmer E, Whittaker E, Lebon P, Stetson DB, Bonthron DT, Crow YJ. 2009. Mutations involved in Aicardi-Goutieres syndrome implicate SAMHD1 as regulator of the innate immune response. Nat Genet 41(7):829-832.

Rice GI, Kasher PR, Forte GM, Mannion NM, Greenwood SM, Szynkiewicz M, Dickerson JE, Bhaskar SS, Zampini M, Briggs TA, Jenkinson EM, Bacino CA, Battini R, Bertini E, Brogan PA, Brueton LA, Carpanelli

M, De Laet C, de Lonlay P, del Toro M, Desguerre I, Fazzi E, Garcia-Cazorla A, Heiberg A, Kawaguchi M, Kumar R, Lin JP, Lourenco CM, Male AM, Marques W, Jr., Mignot C, Olivieri I, Orcesi S, Prabhakar P, Rasmussen M, Robinson RA, Rozenberg F, Schmidt JL, Steindl K, Tan TY, van der Merwe WG, Vanderver A, Vassallo G, Wakeling EL, Wassmer E, Whittaker E, Livingston JH, Lebon P, Suzuki T, McLaughlin PJ, Keegan LP, O'Connell MA, Lovell SC, Crow YJ. 2012. Mutations in ADAR1 cause Aicardi-Goutieres syndrome associated with a type I interferon signature. Nat Genet 44(11):1243-1248.

Uggetti C, La Piana R, Orcesi S, Egitto MG, Crow YJ, Fazzi E. 2009. Aicardi-Goutieres syndrome: neuroradiologic findings and follow-up. AJNR Am J Neuroradiol 30(10):1971-1976.

Voudris KA, Skardoutsou A, Hasiotou M, Theodoropoulos B, Vagiakou EA. 2002. Long-term findings on brain magnetic resonance imaging in acute encephalopathy with bilateral striatal necrosis associated with measles. J Child Neurol 17(10):776-777.

Yamamoto K, Chiba HO, Ishitobi M, Nakagawa H, Ogawa T, Ishii K. 1997. Acute encephalopathy with bilateral striatal necrosis: favourable response to corticosteroid therapy. Eur J Paediatr Neurol 1(1):41-45.

FIGURE LEGENDS

Figure 1: Infantile bilateral striatal necrosis in AGS. **A, B.** Axial head CT scan of Patient 1 (A) and Patient 2 (B), performed at the age of 8 months in both cases, showing bilateral punctate calcifications at the level of the putamina, particularly in their lateral aspect. In Figure 1B a posterior ventricular enlargement is also visible **C.** Axial TSE T2-weighted MR image of Patient 2 at age 3 years showing hyperintense signal at the level of putamina bilaterally and enlargement of the lateral ventricles as a result of caudate atrophy. **D, E.** Coronal T2-FLAIR (D) and axial T2 (E)-weighted MR images of Patient 1 at age 8 months showing inhomogeneous hyperintense signal at the level of the putamina bilaterally and white matter abnormalities in the deep frontal and parieto-occipital regions. To a lesser extent, the caudate and the pallida nuclei appear affected as well. **F.** Axial T2-weighted MR image of Patient 1 at age 11 months showing progressive atrophy of the striata and consequent ventricular enlargement.