

Early-Onset Absence Epilepsy Caused by Mutations in the Glucose Transporter GLUT1

Arvid Suls, MSc,¹⁻³ Saul A. Mullen, MBBS,⁴ Yvonne G. Weber, MD,⁵ Kristien Verhaert, MD,⁶ Bertien Ceulemans, PhD, MD,^{3,6,7} Renzo Guerrini, MD,⁸ Thomas V. Wuttke, MD,^{5,9} Alberto Salvo-Vargas,^{5,9} Liesbet Deprez, PhD,¹⁻³ Lieve R. F. Claes, PhD,¹⁻³ Alben Jordanova, PhD,¹⁻³ Samuel F. Berkovic, MD, FRSc,⁴ Holger Lerche, MD,^{5,9} Peter De Jonghe, PhD, MD,^{1-3,5} and Ingrid E. Scheffer, PhD, MBBS^{4,10}

Absence epilepsies of childhood are heterogeneous with most cases following complex inheritance. Those cases with onset before 4 years of age represent a poorly studied subset. We screened 34 patients with early-onset absence epilepsy for mutations in *SLC2A1*, the gene encoding the GLUT1 glucose transporter. Mutations leading to reduced protein function were found in 12% (4/34) of patients. Two mutations arose de novo, and two were familial. These findings suggest GLUT1 deficiency underlies a significant proportion of early-onset absence epilepsy, which has both genetic counseling and treatment implications because the ketogenic diet is effective in GLUT1 deficiency.

Ann Neurol 2009;66:415–419

Absence epilepsies are an important problem in children. The classic syndrome is childhood absence epilepsy (CAE) where absence seizures typically begin between 4

and 10 years in an otherwise healthy child.^{1,2} CAE is well recognized, although there is ongoing debate regarding the phenotypic limits and precise criteria for diagnosis.^{2,3} For example, some would exclude children with generalized tonic-clonic seizures in addition to absence seizures.^{2,3} Patients with early-onset absence seizures (before 4 years of age) are uncommon and may have more complex phenotypes with additional seizure types, movement disorders, or intellectual impairment.⁴

A disorder apparently unrelated to CAE is encoding the glucose transporter type 1 (GLUT1) deficiency syndrome (GLUT1-DS) classically comprising infantile-onset seizures, complex movement disorders, ataxia, and intellectual disability with microcephaly in some children.⁵ GLUT1-DS is due to heterozygous mutations in *SLC2A1* encoding GLUT1, the molecule transporting glucose across the blood–brain barrier.⁶ Hypoglycorrhachia, caused by impaired glucose transport, is a key diagnostic feature.⁷ Generalized epileptiform spike-wave patterns are seen, and heterogeneous seizure types including absence, myoclonic, and tonic-clonic seizures have been reported, but an homogeneous epilepsy syndrome has not been recognized.⁸ Treatment with the ketogenic diet is effective for seizure control.⁷

More recently, a wider phenotypic spectrum associated with GLUT1 deficiency has been reported including paroxysmal exercise-induced dyskinesia, later onset seizures, often normal intellect, and even normal cerebrospinal fluid (CSF)/serum glucose ratios.^{9–12} Critical review shows that absence seizures, particularly in younger children, emerge as a prominent seizure phenotype.^{8–13} We hypothesized that GLUT1 deficiency may underlie a significant proportion of early-onset absence epilepsies.

Patients and Methods

Patients

Thirty-four patients with onset of absence epilepsy before 4 years of age and no evidence of a secondary cause for their epilepsy were included. This age cutoff is the widely accepted minimum onset age for CAE.¹ All had generalized spike-wave (>2.5Hz) and absence seizures documented on electroencephalogram. Patients with atonic or tonic seizures were excluded. Informed consent was obtained from all patients and, for minors, their parents or legal guardians. Ethics approval for the study was provided by the Human Research Ethics Committee at the participating centers.

Mutation Analysis

Mutation analysis of all exons and intron-exon boundaries of *SLC2A1* was performed on genomic DNA of patients and their parents, when available, by direct sequencing according to procedures described elsewhere.¹² Primer sequences can be obtained on request. To confirm the identified mutations in the patients and their absence in a control population of 276 ethnically matched subjects, we performed pyrosequencing on genomic DNA. Numbering of mutations started at A of the translation initiation codon, ATG, using complementary DNA sequence NM_006516.1.

From the ¹Neurogenetics Group, VIB Department of Molecular Genetics; ²Laboratory of Neurogenetics, Institute Born-Bunge; ³University of Antwerp, Antwerp, Belgium; ⁴Department of Medicine, Epilepsy Research Centre, University of Melbourne, Austin Health, Melbourne, Australia; ⁵Neurological Clinic, University of Ulm, Ulm, Germany; ⁶Division of Neurology and Child Neurology, University Hospital of Antwerp, University of Antwerp, Antwerp; ⁷Epilepsy Center for Children and Youth, Pulderbos, Belgium; ⁸Department of Neurology and Neurosurgery, Children's Hospital A. Meyer, University of Florence, Florence, Italy; ⁹Institute of Applied Physiology, University of Ulm, Ulm, Germany; and ¹⁰Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, Australia.

Current address for Dr Wuttke: MGH-HMS Center for Nervous System Repair, Departments of Neurosurgery and Neurology, Program in Neuroscience, Harvard Medical School; Nayef Al-Rodhan Laboratories, Massachusetts General Hospital; and Department of Stem Cell and Regenerative Biology and Harvard Stem Cell Institute, Harvard University, Boston, MA 02114.

Address correspondence to Dr Scheffer, Epilepsy Research Centre, Level 1, Neurosciences Building, Austin Health, Banksia Street, West Heidelberg, Victoria 3081, Australia. E-mail: scheffer@unimelb.edu.au

Potential conflict of interest: Nothing to report.

A.S., S.A.M., and Y.G.W. contributed equally to this work.

Additional Supporting Information may be found in the online version of this article.

Received Jan 28, 2009, and in revised form Mar 13. Accepted for publication Apr 3, 2009. Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.21724

Table. Clinical and Mutation Details of Early-Onset Absence Epilepsy Patients with GLUT1 Mutations

Patient No.	Sex	Current Age	Age of Onset			Examination			Outcome		Family History of Epilepsy	SLC2A1 Mutations				
			Absence	GTCS	Myoclonus	Motor	Head Circumference	Paroxysmal Dyskinesia Onset	Intellect	Seizure		Location in Gene	DNA Mutation	Protein Mutation	Position in Protein	
1	F	28 yr	3 yr	7 yr	—	Normal	Normal	—	Normal	Seizure free with VPA from 7 years	Yes	Exon 5	c.668G>C	p.R223P	Loop TMD6 and TMD7	
2	M	28 yr	3 yr	8 yr	—	Mild upper limb ataxia	Normal	—	Mild ID (IQ, 56)	Daily absences on VPA + TPM	Yes	Exon 7	c.971C>T	p.S324L	TMD8	
3	F	12 yr	14 mo	—	14 mo	Mild gait ataxia	Normal	Subtle, 5 yr	Moderate ID (IQ, 48)	Sporadic absences on VPA + LTG	No	Exon 4	c.376C>T	p.R126C	TMD4	
4	F	7 yr	13 mo	12 mo	—	Normal	Normal	—	Normal	(IQ78)	Frequent absences on VPA+LTG+ETX	No	Intron 5	c.680-11G>A	p.227-228ins PPV	Loop TMD6 and TMD7

DNA mutations were numbered using the reference sequence NM_006516.1.

GTCS = generalized tonic-clonic seizure; VPA = valproic acid; TMD = transmembrane domain; ID = intellectual disability; IQ = intelligence quotient; TPM = topiramate; LTG = lamotrigine; ETX = ethosuximide.

RNA Isolation and Reverse Transcription Polymerase Chain Reaction

Total RNA of the patient with the intronic mutation, c.680-11G>A, and her mother was isolated from lymphoblast cell lines using the RNeasy kit (Qiagen, Venlo, the Netherlands). After synthesis of first-strand complementary DNA with Superscript III First-Strand Synthesis System for reverse transcription polymerase chain reaction (Invitrogen, Carlsbad, CA), we performed polymerase chain reaction amplification using primers annealing in *SLC2A1* exons 4 and 8. Wild-type and aberrant polymerase chain reaction fragments were subsequently sequenced according to procedures described elsewhere.¹²

Functional Studies in *Xenopus* Oocytes

All experimental procedures have been described previously.¹¹ In brief, the QuickChange kit (Stratagene, La Jolla, CA) was used to introduce mutations in the complementary DNA of *SLC2A1* (pSP65 plasmid kindly provided by Dr Mike Mueckler¹⁴). The desired mutations were verified and other mutations excluded by sequencing all mutated clones completely. Plasmids were linearized and transcribed in vitro (Sp6 mMessageMachine kit; Ambion, Austin, TX). Messenger RNA was injected into oocytes to study glucose uptake by zero-trans influx experiments with 3-O-methyl-D-glucose, and protein stability and surface expression using Western blots and immunocytochemistry (rabbit anti-GLUT1 antibody; Abcam, Cambridge, MA).

Results

Mutations were identified in 4 of 34 (12%) patients with early-onset absence epilepsy (Table). No clinical differences were observed between mutation-positive and -negative patients for age of onset, intellectual outcome, and electroclinical syndrome. On clinical review, after discovery of a *SLC2A1* mutation, Patient 3 was found to have mild paroxysmal exercise-induced dyskinesia, previously considered an epileptic phenomenon. Subtle ataxia

was found in Patients 2 and 3, possibly explained by high-dose antiepileptic drugs.

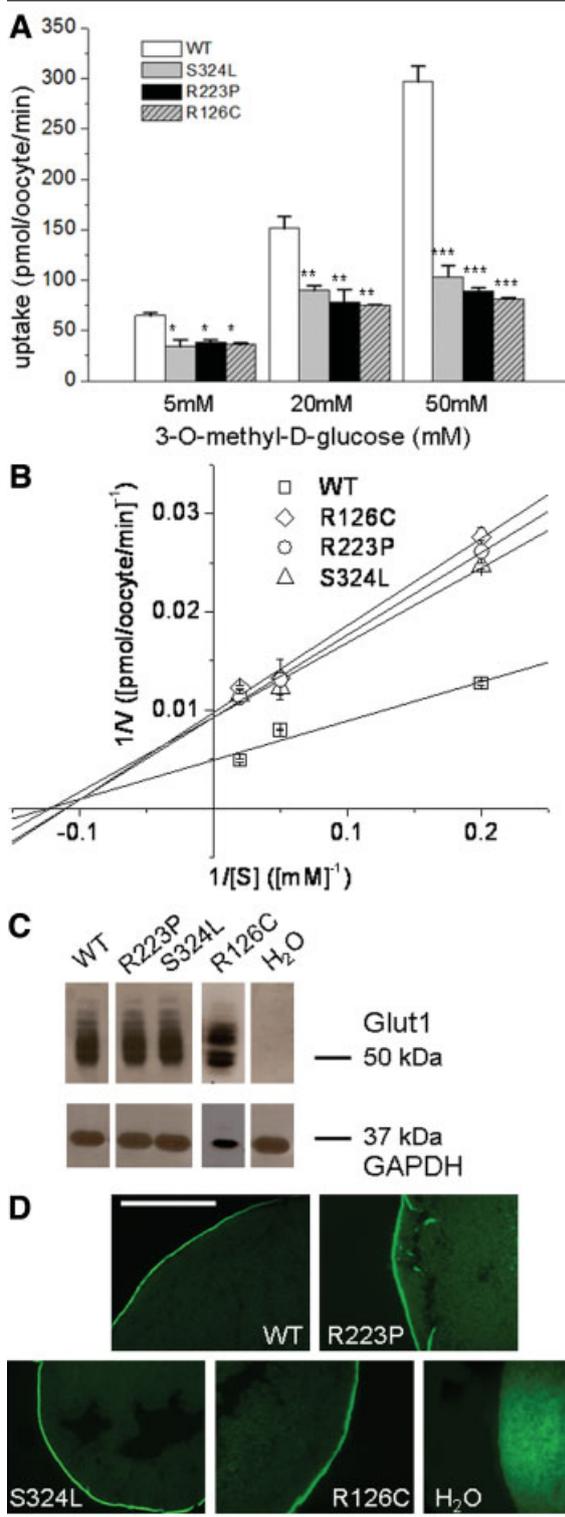
Three exonic missense mutations and one intronic splice-site mutation were identified (see the Table). Patients 1 and 2 inherited their missense mutations from a parent with idiopathic epilepsy, that is, juvenile absence epilepsy and adult-onset absence epilepsy. Examination of parental DNA of Patients 3 and 4 did not show the mutation, suggesting that the mutation in these children arose de novo (paternity was confirmed with a panel of 31 STR markers located on 15 different chromosomes). None of the 4 mutations was observed in 276 ethnically matched control subjects. In GLUT1-DS, different substitutions for R126 have been identified, including the cysteine substitution found here. Previous functional studies suggested that this substitution was pathogenic.¹⁵ R126 and S324 are highly conserved amino acids in different species. R223 is conserved only in mammals, but substitution of this polar by a nonpolar amino acid (proline), as found in our patient, is not observed in evolution (alignments in supplementary data).

Because the intronic mutation creates a new splice acceptor site, we assessed its effect on messenger RNA splicing using lymphoblast cell lines of the patient and her unaffected mother. An aberrant *SLC2A1* transcript was demonstrated only in the patient. We observed an in-frame 9-base pair insertion, TCCCCCAG, in front of exon 6, indicating that the intronic mutation results in the utilization of a cryptic splice acceptor site within intron 5. The mutation predicts the insertion of three amino acids PPV in the loop connecting transmembrane domains 6 and 7.

Functional Investigations of Mutant and Wild-Type GLUT1 Transporters

Glucose transport was decreased for all three GLUT1 missense mutations compared with wild type (Fig. A). All mutations markedly decreased the maximum transport velocity, V_{max} , without significantly affecting the

Michaelis–Menten constant, K_m (see Fig. B). There was no evident defect in production and stability of the mutant proteins (see Fig. C) or insertion in the cell-surface membrane (see Fig. D). Thus, all missense mutations reduced the transport capacity of GLUT1, probably without affecting glucose binding, protein stability, or intracellular transport mechanisms.



Discussion

SLC2A1 mutations were found in 12% of this cohort of 34 patients with early-onset absence epilepsy. The pathogenicity of these mutations is strongly suggested by the high conservation of the altered amino acids, the absence of these mutations in control subjects, the de novo occurrence of two of the mutations, and the in vitro studies showing a functional deficit of glucose transport for the three missense mutations. Because CSF measures are not routinely performed in milder generalized epilepsies, no CSF/serum glucose ratios were available for our patients. Also, it has recently been shown that, in patients with GLUT1 deficiency with milder phenotypes such as paroxysmal exercise-induced dyskinesia, the CSF/serum glucose ratio can be borderline or even normal.^{11,12}

The patients' epilepsy was characterized by absence seizures as the predominant seizure type, onset before 4 years of age, and normal development before seizure on-

*Fig. Functional studies of wild-type (WT) and mutant GLUT1 transporters in Xenopus oocytes. (A) Reduced glucose uptake recorded by zero-trans-influx experiments in oocytes injected with mutant compared with WT complementary RNA (cRNA). Shown are representative results recorded from 3×10 oocytes for each data point: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. White bars represent wild type; gray bars represent S324L; black bars represent R223P; and hatched bars represent R126C. (B) Kinetic analysis of glucose uptake in oocytes according to Lineweaver–Burk. Lines represent linear fits to the data points. V_{max} and K_m were calculated from the y- and x-interceptions of the linear fit, respectively, as the y-intercept equals $1/N_{max}$ and the x-intercept represents $-1/K_m$. V_{max} was significantly reduced for all three point mutations compared with the WT without obvious effects on K_m (WT: $V_{max} = 202 \pm 49$, $K_m = 8.1 \pm 3.7$; R126C: $V_{max} = 103 \pm 11$, $K_m = 9.1 \pm 1.8$; R223P: $V_{max} = 108 \pm 5$, $K_m = 9.0 \pm 0.7$; S324L: $V_{max} = 108 \pm 11$, $K_m = 8.2 \pm 1.6$). Squares represent wild type; triangles represent S324L; circles represent R223P; and diamonds represent R126C. (C) Western blots obtained from oocytes injected with equal amounts of cRNA demonstrated similar bands for all mutations and the WT, but no respective band for oocytes injected with H₂O as a negative control. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as a loading control. (D) Immunocytochemical analysis of injected oocytes using an anti-GLUT1 antibody demonstrated similar staining of the surface membranes for all four clones, but not for water-injected oocytes, suggesting normal trafficking of the mutant proteins to the surface membrane. The scale bar indicates 100 μ m.*

set. The epilepsy varied from being easily controlled in some to refractory in others; intellect ranged from normal to moderately impaired. Thus, the seizure phenotype cannot be readily distinguished from CAE except for the earlier age of onset. Ataxia and dyskinesia, both mild, were diagnosed only in hindsight. Mild ataxia and intellectual disability were not exclusive to patients with *SLC2A1* mutations (see Supplementary Table).

The ketogenic diet offers an alternative treatment because it is effective for seizures in classic GLUT1-DS. Although cognitive difficulties respond less well, improvement of intellectual abilities has been observed.^{7,11} Preliminary results of the ketogenic diet in Patients 3 and 4 showed a marked reduction of epileptiform activity on electroencephalogram.

Absence epilepsies usually follow complex inheritance where multiple genes are thought to contribute to the cause. The risk to first-degree relatives is about 8%.¹⁶ In contrast, the majority of patients with classic GLUT1-DS are isolated and the mutations arise de novo, meaning that the risk to siblings is negligible, as also found in two of four patients here with early-onset absence epilepsy. However, the milder, more recently recognized phenotypes with *SLC2A1* mutations may be associated with autosomal dominant transmission with high penetrance. Thus, the risk to first-degree relatives approaches 50%, as observed in the other two patients. A molecular diagnosis of a *SLC2A1* defect in a child with absence epilepsy, with subsequent investigation of the family, now allows accurate genetic counseling together with early diagnosis and treatment. Rarer identified molecular causes of early-onset absence epilepsy include mutations in a gene encoding a GABA receptor subunit (*GABRG2*) and a sodium channel subunit gene (*SCN1B*).^{17,18}

Molecular diagnosis for epilepsy has been a research tool until now with the exception of sodium channel mutations in Dravet syndrome where 70% to 80% of patients have mutations.^{19,20} Here we report the second gene with wide diagnostic utility for an idiopathic epilepsy syndrome. Therefore, we suggest that *SLC2A1* mutational analysis is warranted in all children with absence seizures beginning before 4 years of age, enabling a molecular diagnosis with treatment and genetic counseling implications.

This research was supported by the EU Sixth Framework Thematic Priority Life Sciences, Genomics and Biotechnology for Health, contract number LSH-CT-2006-037315 (EPICURE) R.G. NHMRC Postgraduate Research Scholarship (ID 454829) S.A.M. NHMRC Program Grant (ID: 400121). I.E.S. & S.F.B. Federal Ministry for Education and Research in Germany (BMBF/NGFNplus: 01GS08123, to H.L.), European Union (Epicure: LSH 037315) H.L. Fellowship, University Antwerp A.S. Fellowship FWO-F L.R.F.C.

We thank the patients and their families for their kind cooperation and participation in this study. We ac-

knowledge the contribution of T. Van Dyck, T. Deconinck, and the VIB Genetic Service Facility (<http://www.vibgeneticservicefacility.be>) to the genetic analyses.

References

- Loiseau P, Panayiotopoulos CP. ILAE classification: epilepsy syndromes and related conditions—childhood absence epilepsy. Available at: http://www.ilae-epilepsy.org/Visitors/Centre/ctf/syn_frame.html. Accessed 18th January 2009.
- Hirsch E, Panayiotopoulos CP. Childhood absence epilepsy and related syndromes. In: Roger J, Bureau M, Dravet C, et al, eds. Epileptic syndromes in infancy, childhood and adolescence. 4th ed. Montrouge, France: John Libbey Eurotext, 2005:315–335.
- Sadleir LG, Farrell K, Smith S, et al. Electroclinical features of absence seizures in childhood absence epilepsy. *Neurology* 2006;67:413–418.
- Guerrini R, Sanchez-Carpintero R, Deonna T, et al. Early-onset absence epilepsy and paroxysmal dyskinesia. *Epilepsia* 2002;43:1224–1229.
- De Vivo DC, Trifiletti RR, Jacobson RI, et al. Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. *N Engl J Med* 1991;325:703–709.
- Seidner G, Alvarez MG, Yeh JI, et al. GLUT-1 deficiency syndrome caused by haploinsufficiency of the blood-brain barrier hexose carrier. *Nat Genet* 1998;18:188–191.
- Klepper J, Leidencker B. GLUT1 deficiency syndrome—2007 update. *Dev Med Child Neurol* 2007;49:707–716.
- Leary LD, Wang D, Nordli DR Jr, et al. Seizure characterization and electroencephalographic features in Glut-1 deficiency syndrome. *Epilepsia* 2003;44:701–707.
- Brockmann K, Wang D, Korenke CG, et al. Autosomal dominant glut-1 deficiency syndrome and familial epilepsy. *Ann Neurol* 2001;50:476–485.
- Friedman JR, Thiele EA, Wang D, et al. Atypical GLUT1 deficiency with prominent movement disorder responsive to ketogenic diet. *Mov Disord* 2006;21:241–245.
- Weber YG, Storch A, Wuttke TV, et al. GLUT1 mutations are a cause of paroxysmal exertion-induced dyskinesias and induce hemolytic anemia by a cation leak. *J Clin Invest* 2008;118:2157–2168.
- Suls A, Dedeken P, Goffin K, et al. Paroxysmal exercise-induced dyskinesia and epilepsy is due to mutations in *SLC2A1*, encoding the glucose transporter GLUT1. *Brain* 2008;131:1831–1844.
- Roulet-Perez E, Ballhausen D, Bonafe L, et al. Glut-1 deficiency syndrome masquerading as idiopathic generalized epilepsy. *Epilepsia* 2008;49:1955–1958.
- Mueckler M, Caruso C, Baldwin SA, et al. Sequence and structure of a human glucose transporter. *Science* 1985;229:941–945.
- Wong HY, Law PY, Ho YY. Disease-associated Glut1 single amino acid substitute mutations S66F, R126C, and T295M constitute Glut1-deficiency states in vitro. *Mol Genet Metab* 2007;90:193–198.
- Helbig I, Scheffer IE, Mulley JC, Berkovic SF. Navigating the channels and beyond: unravelling the genetics of the epilepsies. *Lancet Neurol* 2008;7:231–245.
- Audenaert D, Claes L, Ceulemans B, et al. A deletion in *SCN1B* is associated with febrile seizures and early-onset absence epilepsy. *Neurology* 2003;61:854–856.
- Marini C, Harkin LA, Wallace RH, et al. Childhood absence epilepsy and febrile seizures: a family with a GABA(A) receptor mutation. *Brain* 2003;126:230–240.

19. Claes L, Del Favero J, Ceulemans B, et al. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. *Am J Hum Genet* 2001;68:1327–1332.
20. Harkin LA, McMahon JM, Iona X, et al. The spectrum of SCN1A-related infantile epileptic encephalopathies. *Brain* 2007;130:843–852.

SLC25A19 Mutation as a Cause of Neuropathy and Bilateral Striatal Necrosis

Ronen Spiegel, MD,^{1–4} Avraham Shaag, PhD,¹ Simon Edvardson, MD,⁵ Hanna Mandel, MD,^{4,6} Polina Stepensky, MD,¹ Staviv A. Shalev, MD,^{3,4} Yoseph Horovitz, MD,^{2,4} Ophry Pines, PhD,⁷ and Orly Elpeleg, MD¹

Four patients, aged 7–20 years, suffered from recurrent episodes of flaccid paralysis and encephalopathy associated with bilateral striatal necrosis and chronic progressive polyneuropathy. Using homozygosity mapping, a pathogenic missense mutation in the *SLC25A19* gene that encodes the mitochondrial thiamine pyrophosphate transporter was identified. An *SLC25A19* mutation was previously reported in Amish congenital lethal microcephaly but the present patients' phenotype is markedly different, with normal head circumference, normal early childhood development, age-appropriate cognitive skills, and normal urinary organic acid profile. Determination of the *SLC25A19* sequence should be considered in patients with bilateral striatal necrosis and progressive polyneuropathy.

Ann Neurol 2009;66:419–424

Acute basal ganglia necrosis in the pediatric age group is a neurological disorder characterized by symmetrical

From the ¹Department of Human Genetics and Metabolic Diseases, Hadassah–Hebrew University Medical Center, Jerusalem, Israel; ²Pediatric Department A and ³Genetic Institute, Ha'Emek Medical Center, Afula, Israel; ⁴Rappaport School of Medicine, Technion, Haifa, Israel; ⁵Pediatric Neurology Unit, Hadassah–Hebrew University Medical Center, Jerusalem, Israel; ⁶Metabolic Unit, Mayer Medical Center, Rappaport School of Medicine, Technion, Haifa, Israel; and ⁷Department of Microbiology and Molecular Genetics, Institute of Medical Research (IMRIC), Hebrew University, Jerusalem, Israel

Address correspondence to Prof. Orly Elpeleg, Department of Human Genetics and Metabolic Diseases, Hadassah–Hebrew University Medical Center, Jerusalem 91120, Israel. E-mail: Elpeleg@cc.huji.ac.il

Potential conflict of interest: Nothing to report.

Received Mar 14, 2009, and in revised form Apr 30. Accepted for publication May 8, 2009. Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.21752

degeneration of the caudate nucleus, putamen, and occasionally the globus pallidus. It is typically preceded by an intercurrent febrile illness and is clinically manifested by truncal ataxia and hypotonia, transient limb paresis or fixed dystonic posturing, hyporeflexia, and a change in consciousness level.^{1,2} Sucking and swallowing are usually impaired but respiration is generally unaffected. The acute phase lasts days to weeks and in the sporadic patients, clinical recovery is often complete, though persistence of behavioral and movement symptoms and mild learning disabilities are sometimes seen.

The outcome is less favorable for the familial cases in which the course is relentlessly progressive or punctuated by recurrent episodes with involvement of additional brain regions and significant residual neurological damage. The differential diagnosis of the latter group includes mitochondrial respiratory chain defects mainly due to mutations in the *ATP6* gene,³ organic acid disorders,⁴ Wilson disease,⁵ juvenile Huntington's chorea,⁶ pantothenate kinase-associated neurodegeneration,⁷ biotin responsive basal ganglia disease,⁸ and the striatal necrosis associated with *NUP62* mutation.⁹

We now report on the study of four patients who suffered from recurrent episodes of flaccid paralysis and encephalopathy associated with bilateral striatal necrosis.

Case Reports

An Illustrative Case

Patient II-1, 20 years old, is the oldest of five children born to consanguineous parents. Pregnancy, delivery, postnatal course, and early psychomotor development were all normal. At the age of 3.5 years, on the second day of a nonspecific upper respiratory infection, the patient became obtunded and weak over the course of few hours. On initial examination he was difficult to arouse, disoriented, and his speech was slurred. Proximal and distal muscle weakness was noted (biceps and shoulder abductor strength was 3/5). The patient could not rise and this was associated with decreased strength of the plantar extensors and flexors (3/5 bilaterally). Deep tendon reflexes could not be elicited. Oral feeding was unsuccessful due to choking and nasogastric tube feeding was required. Over the course of 3 weeks, muscle strength and deep tendon reflexes returned to normal. Residual effects included difficulty with opening of tight jars and occasional falls attributed to minimal distal weakness. Cognitive functions returned to normal and there was no subsequent loss of milestones or developmental delay.

Thereafter, the patient remained in good health, started school at the appropriate age, and had no limitations in his daily activities. Beginning at 7 years of age, he was noted to have increasing difficulty with long distance walking, he fell frequently, complained of