Unfortunately, there is no effective treatment for this disorder. Considering the relatively high association with epilepsy in this disease and the prolonged febrile seizures in our patient, we discussed starting anticonvulsive therapy, but, so far, the parents remain undecisive. The current therapeutic regimen for our patient is therefore limited to early seizure management with oral or rectal benzodiazepines, and in case neurologic symptoms should appear in the future, beginning early supportive therapy.1

The key features of our 9-month-old female patient were symptoms fitting hemiclonal-hemiplegia-epilepsy syndrome.2 Hemiclonal-hemiplegia-epilepsy syndrome is characterized by a febrile illness in a child younger than 4 years and prolonged clonic seizures with unilateral predominance, followed by the development of hemiplegia. Neuroradiologic studies might show edematous swelling of one hemisphere at the time of the initial convulsive status. The incidence of the syndrome has declined considerably in industrialized countries over the past 15 years, most likely owing to more effective management of status epilepticus.

To our knowledge, acute hemiclonal-hemiplegia-epilepsy syndrome has not been reported as a first symptom in L-2-hydroxyglutaric aciduria. Although febrile seizures have been found retrospectively in the early course of this disease, the majority of cases were often diagnosed years later with manifestations of psychomotor developmental delay, epilepsy, or early course of this disease. The majority of cases were often diagnosed years later with manifestations of psychomotor developmental delay, epilepsy, or early course of this disease. The majority of cases were often diagnosed years later with manifestations of psychomotor developmental delay, epilepsy, or early course of this disease.

In conclusion, we present a patient with hemiclonal-hemiplegia-epilepsy syndrome as a presenting feature of L-2-hydroxyglutaric aciduria. In patients with hemiclonal-hemiplegia-epilepsy syndrome, in particular when associated with macrocephaly, central nervous system imaging and a diagnostic work-up for organic acidurias are recommended. As long as the pathogenesis of the progressive mental impairment in patients with L-2-hydroxyglutaric aciduria remains obscure, we advocate early diagnosis and therapeutic approach of prolonged febrile seizures in patients with L-2-hydroxyglutaric aciduria to avoid potential long-term sequelae such as mesial temporal lobe epilepsy or hippocampal sclerosis, which might further contribute to the psychomotor disturbances in affected patients.13,14

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Diagnosis and Molecular Characterization of Non-classic Forms of Tay-Sachs Disease in Brazil

ABSTRACT

Molecular analysis of five Brazilian families, including eight patients presenting with nonclassic Tay-Sachs disease, was performed to identify frequent causative mutations and their correlation with clinical course. Three patients were affected by the B1 subacute variant and were shown to carry the R178H mutation (the DN allele), which is also common among Portuguese patients. Two of them were compound heterozygotes, whereas the third presented with the mutation in both alleles. Since Brazil was a Portuguese colony for over two centuries, common ancestry might be the probable explanation. The fourth patient presented with a juvenile phenotype and carries the R499H mutation, which has been reported only once worldwide and is associated with residual enzyme activity, responsible for a slower clinical course. The fifth family, of an Ashkenazi Jewish background, showed an extensive intrafamilial clinical variability among three affected sibs presenting with muscle atrophy, ataxia, and psychiatric symptoms. They were first diagnosed as having atypical spinal muscular atrophy and, subse-

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patients 5, 6, and 7 are siblings; patient 8 is their first cousin (see Figure 1). Patient number is as in the text.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>First Signs/Age at Appearance</th>
<th>Genotype</th>
<th>TSD Variant</th>
<th>Ancestry Background</th>
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<tbody>
<tr>
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<td>R178H/7</td>
<td>B1 (subacute; late infantile form)</td>
<td>Portuguese/Italian</td>
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<tr>
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<td>R178H/7</td>
<td>B1 (subacute; late infantile form)</td>
<td>Portuguese/Italian</td>
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<tr>
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<td>6</td>
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<td>R178H/R178H</td>
<td>B1 (subacute; late infantile form)</td>
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<tr>
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<td>R499H/7</td>
<td>B1 (subacute; late infantile form)</td>
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</tr>
<tr>
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<td>Chronic; adult form</td>
<td>Ashkenazi J ewish</td>
</tr>
<tr>
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<td>Ashkenazi J ewish</td>
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<tr>
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<td>32</td>
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<td>G2695/Ins-TAC1278</td>
<td>Chronic; adult form</td>
<td>Ashkenazi J ewish</td>
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<td>Suicide at age 24 yr</td>
<td>Not performed</td>
<td>Chronic; adult form?</td>
<td>Ashkenazi J ewish</td>
</tr>
</tbody>
</table>

TSD = Tay-Sachs disease.

Patient number is as in the text.

* Patients 5, 6, and 7 are siblings; patient 8 is their first cousin (see Figure 1).

DNA analysis included HEXA gene mutations InsTAC1278, IVS12+1g>c, G2695, IVS7+1g>c, and R178H.

A Tay-Sachs disease is an autosomal recessive disease of lysosome storage characterized by progressive neurologic degeneration (Mendelian Inheritance in Man 272800). Children affected by the classic form manifest the first symptoms around 6 months of age and develop a rapidly progressive neurodegenerative disease, culminating in death before 5 years of age. Tay-Sachs disease is caused by mutations in the HEXA gene (chromosome 15q23-q24), coding for the α subunit of the enzyme β-hexosaminidase A. In the absence of the enzyme, its substrate, GM2 ganglioside, accumulates progressively in the neurons of the central nervous system. Rare variant phenotypes of nonclassic Tay-Sachs disease include the chronic, late-onset form and a subacute form with a late-infantile or juvenile presentation. These less severe phenotypes are due to residual enzyme activity. In the late-onset Tay-Sachs form, the first clinical signals can occur during the first or second decade of life and disease progression is slow. Neurologic manifestation and severity are variable and can include proximal muscle weakness, cramping and wasting, unsteady gait, ataxia, hand tremors, dysarthria, dystonia, and/or dyskinesia. Psychiatric abnormalities include schizophrenia, agitation, delusions, hallucinations, paranoia, and recurrent depression. In the juvenile form, an intermediate clinical presentation and survival into adolescence or adulthood are observed. Another rare phenotype is the B1 variant of Tay-Sachs disease, in which the hexosaminidase A structure is intact but mutations affecting the enzyme’s active site prevent catalytic activity against its natural substrate, G, ganglioside, and against the sulfated form of the artificial substrate, sulfated 4-methylumbelliferyl-2-acetamido-2-deoxy-beta-D-glucopyranoside (4MUGS), used for biochemical diagnosis. The B1 variant cases present with late-infantile disease onset, and, to date, there are less than one hundred bibliographic references to this condition in MEDLINE. Most cases are from northern Portugal.

Molecular analysis of five nonconsanguineous Brazilian families presenting with nonclassic Tay-Sachs disease was performed to identify frequent causative mutations and to correlate them with the clinical course observed in the patients. Table 1 shows a summary of the patients and their main disease characteristics. We searched for the three Jewish (InsTAC1278, IVS12+1g>c and G2695) and the two Brazilian (Portuguese (IVS7+1g>c and R178H) most frequent mutations. Complete gene sequencing was performed in one of the subjects (patient 4).

Three unrelated patients (see Table 1, patients 1 to 3) have a B1 phenotype, confirmed by MUGS hexosaminidase A-reduced activity. They all presented with acoustic startle in the first year of life, but gait disturbance and cognitive decline were the symptoms that brought them to medical attention, at 2 to 3 years of age. Macular cherry-red spot was present in patients 1 and 2 but not in patient 3.

Patients 1 and 2, currently 3 and 4 years of age, have progressive neurologic deterioration with spasticity, visual and cognitive decline, and epileptic seizures. They are compound heterozygotes presenting with the R178H mutation (also called the DN allele) with a second unidentified mutation. Patient 3, who is currently 5 years old, lost the ability to walk in the last year and is currently bedridden, with severe dystonic features and epileptic seizures. She is homozygous for the R178H mutation, and her clinical course was similar to that of other previously reported homozygotes. This mutation is associated with the Tay-Sachs disease B1 phenotype, and its highest frequency occurs in northern Portugal, from where it has been suggested to originate. Since Brazil was a Portuguese colony for over two centuries, common ancestry might be the best explanation for the presence of the R178H mutation. In fact, all three families have a mixed origin, including an important Portuguese background. Interestingly, also among Brazilian patients with classic Tay-Sachs disease, a mutation described in Portuguese patients (IVS7+1g>c) is the most prevalent. Patient 4 has a juvenile (not B1) form of the disease and presented with gait disturbance as the first clinical sign between 1 and 2 years of age followed by cognitive decline. Acoustic startle was an early sign, but cherry-red macular spot never occurred. Presently, the patient is 9 years old and losing acquired characteristics, such as speech and walking. His clinical manifestation is less severe than that observed in patients 1, 2, and 3.
ing of the HEXA gene disclosed the R499H mutation in heterozygosity, with the second mutation remaining unidentified. The R499H mutation was described in one patient affected by the subacute form of Tay-Sachs disease, who survived to the age of 26 years and was a compound heterozygote with a functionally null second allele. The R499H mutation conferred a 3% residual enzyme activity, and it probably warrants a slower disease progression, also in patient 4.

Patients 5, 6, and 7 are siblings of Ashkenazi Jewish ancestry (Figure 1), presenting with a remarkable intrafamilial clinical variability. Their phenotype includes muscle weakness, gait disturbance, speech abnormalities, and psychiatric symptoms but no sensory alterations. Hearing and vision are normal, and no cherry-red spots on maculae can be seen. They all attended college, but disease progression impeded conclusion for two of them. The propositus (patient 5) was recognized as clumsy since 6 to 7 years of age and reported cramps and frequent “falls” associated with difficulty in running or jumping during exercises (physical practice) in infancy. His speech was badly articulated and sometimes incomprehensible. He has been wheelchair bound since age 27 years, and currently, at age 37 years, tremors and fasciculation are also observed. The oldest of his two sisters is 35 years old, and her disease signals started at 9 years of age, with dysarthria, followed by a slowly progressive gait instability and global weakness, associated with several psychotic outbreaks, hallucinations, and extreme anxiety. The youngest sister also had disease signals at age 10 years, but now, at 32 years of age, she is showing only mild proximal motor deficiency in the lower limbs and is significantly less affected than her sibs.

Three affected patients in the same family were reported in 1976, and the observation of a homogeneous phenotype led to the suggestion that the clinical course tended to be consistent within each family. Later studies, however, observed variation in the phenotype among siblings in some families. The cases herein ascertained confirm that intrafamilial clinical variability might be present in late-onset Tay-Sachs disease, in spite of the uniform clinical manifestation observed in the classic infantile form. As observed for other monogenic conditions, it is possible that late-onset Tay-Sachs disease is inherited in a mendelian fashion, but disease manifestation is a complex trait.

For over 10 years, these three siblings were misdiagnosed. Initially, atypical type III spinal muscular atrophy was suggested based on the results of electromyography and muscle biopsy. Subsequently, the diagnosis of spinocerebellar ataxia was considered, based on the clinical phenotype of the index case. A recent clinical reevaluation by one of us (F.K.) raised the suspicion of late-onset Tay-Sachs disease, which was confirmed based on reduced plasma hexosaminidase A activity and molecular analysis disclosing the G269S and InsTATC1278 mutations, inherited from the father and the mother, respectively (Figure 2). Differential diagnosis helped establish a proper antipsychotic medication for the three sibs since major neuroleptic drugs can considerably worsen the basic disease.

Figure 1. Genealogy from the Ashkenazi Jewish family showing the segregation of the two mutations. Patients III–3, III–5, III–6, and III–7 are patients 8, 5, 6, and 7 in Table 1, respectively.

Figure 2. Visualization of the results of DNA analysis of mutations G269S and InsTATC1278 in 12% polyacrylamide gel in the Ashkenazi Jewish family. The restriction fragment sizes are expressed in base pairs (bp) beside each band. Strategies used are in accordance with Triggs-Raine et al. The strategy for detecting mutation InsTATC1278 is based on the formation of a heteroduplex owing to the 4 bp insertion, which forms the band above the normal 169/173 bp band. The strategy for detecting mutation G269S requires endonuclease digestion with four units of EcoR II for 4 hours. In the absence of the mutation, the normal 167 polymerase chain reaction (PCR) product is cleaved in fragments of 99 and 44 bp, which are visualized in the gel plus two fragments of 16 and 8 bp, which are not visualized. The presence of the mutation abolishes a restriction site, and the 167 bp PCR fragment is cleaved into 99, 52, and 16 bp fragments. Both strategies contain positive heterozygote (Aa) controls, as indicated (C). Samples are numbered according to the pedigree in Figure 1.
Genetic counseling disclosed a first paternal cousin (Figure 1, iii-3) who committed suicide at the age of 24 years and presented with some clinical signals of the disease, including depression (patient B). Other reports have shown an increased risk of suicide among patients with late-onset Tay-Sachs disease. The parents of patient B were tested and shown to carry the G2695 (paternal) and InsTATC1278 (maternal) mutations, suggesting that it was, indeed, a probable undiagnosed case of late-onset Tay-Sachs disease, highlighting the effect of the intramolecular clinical variability in delaying diagnosis.

The frequency of heterozygotes for HEXA mutations in the Jewish population is around 1 in 31 individuals, and the Jewish population of Brazil has a similar carrier frequency. In the Jewish family studied here, the two fathers were brothers, whereas the two mothers, although unrelated, were both Ashkenazi Jewish. Thus, the risk of recessive disorders involved in marriages within some populations is clearly illustrated in this family and emphasizes the importance of Tay-Sachs disease heterozygote screening programs in at-risk populations. In fact, another relative in the family had been identified as a carrier of the InsTATC1278 mutation in a heterozygote screening program prior to the disclosure of the diagnosis in the affected members, but the information was not shared among the family (see Figure 1, III-1). Since it might anticipate diagnosis and considering current efforts to establish a treatment for this form of Tay-Sachs disease, it is advisable that screening programs encourage families to share genetic information. Moreover, owing to the late-onset nature of the disease, early identification of homozygote children is important for genetic counseling of carrier couples. Actually, because prevention still remains the best approach to this disease, individuals of reproductive age in the family were invited for counseling. Five of the tested individuals were shown to be carriers of one of the mutations that segregate in the family, and screening for carrier status was offered to their spouses. In these cases, biochemical analysis is the method of choice, allowing the identification of carrier status owing to any mutation in the gene independent of the ethnic background. No other carrier couple was found in the extended family.

Several studies emphasize the low incidence of late-onset Tay-Sachs disease worldwide, with fewer than 100 published cases. It is interesting to speculate whether many patients could be undiagnosed. Actually, some patients with late-onset Tay-Sachs disease have been misdiagnosed with spinocerebellar ataxias, Kugelberg-Welander syndrome, spinal muscular atrophy, or amyotrophic lateral sclerosis. The family with late-onset Tay-Sachs disease reported here also illustrates the difficulties in establishing the diagnosis in a scenario of clinical variability and overlapping symptoms. Testing patients with atypical spinocerebellar atrophy type III for Tay-Sachs disease, especially if neurogenic symptoms are accompanied by ataxia or psychiatric manifestations, is therefore highly recommended.

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Functional Brain Imaging in Sydenham’s Chorea

To the Editor: Dr Citak and colleagues have reported that functional brain imaging using 99mTc-HMPAO single photon emission computed tomography (SPECT) detected perfusional abnormalities in the basal ganglia in seven cases with Sydenham’s chorea.1 These abnormalities were hyperperfusion in two patients and hypoperfusion in five patients. They suggested that a hyperperfused striatum and thalamus could be indicators of a poor prognosis in Sydenham’s chorea because the patient with hyperperfusion had a poor response to conventional therapy.

There are few reports on brain SPECT used in cases of Sydenham’s chorea. Lee et al reported a case showing hyperperfusion of the basal ganglia at the acute phase and improvement of this at the recovery phase.2 Dilenge et al reported two cases showing hyperperfusion.3 The control SPECT study at the recovery phase had been performed in one of these cases and improvement in the hyperperfusion had been seen. Barsottini et al reported 10 cases, 6 of which showed hyperperfusion of the basal ganglia (the others were normal), but repeated SPECT study at the recovery phase could not be performed.4 Two other studies performed by positron emission tomography (PET), a neurofunctional imaging technique like SPECT, revealed hypermetabolism in the striatum for two cases.5,6 Hypermetabolism returned to normal at the recovery phase for both cases. Hill et al reported a case showing no abnormality,7 and Heye et al reported a case showing hyperperfusion in the striatum in a SPECT study.8 In our study, brain SPECT indicated hyperperfusion in the basal ganglia and thalamus in 16 of 17 patients.9 Also, the radioactivity uptake of the basal ganglia and thalamus, shown as quantitative, at the acute phase was statistically higher than the control group. The control SPECT study, performed in six patients, indicated improvement at the recovery phase in five patients. Only one patient showed no abnormality in both the acute and recovery phases. In 41 patients with Sydenham’s chorea reported in the literature, together with the cases of Dr Citak and colleagues,1 hyperperfusion has been detected in 29 (70.7%) and hypoperfusion in 6 (14.6%) and no perfusional abnormalities in 6 (14.6%) patients. Both the hyperperfusion sign at the control scan and/or the clinical symptoms of patients with Sydenham’s chorea with the hyperperfusion sign improved in all patients.

For neurodegenerative disorders of the basal ganglia causing chorea, a number of studies have been performed with PET and SPECT. Of these, Parkinson disease,10 Wilson disease,11 Huntington chorea,12 Lesch-Nyhan syndrome,13 and benign hereditary chorea14 showed striatal hyperperfusion. Therefore, the hyperperfusion sign seems to be a sign of more permanent dysfunction of the basal ganglia. Nevertheless, hyperperfusion, detected in Sydenham’s chorea,15 has not been a sign of a poorer prognosis.

In the neuropathologic studies of patients with Sydenham’s chorea, lesions extending from inflammation up to degeneration were revealed in the brain cortex and other brain sites, especially the basal ganglia.9 These lesions probably follow one another in a chronologic line. The perfusional abnormalities can change according to these lesions. In addition, the subject of whether hypo- or hyperperfusion will influence anything in the long-duration follow-up or recurrences needs new studies.

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