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ATYPICAL PRESENTATION OF LATE-ONSET TAY-SACHS DISEASE

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Abstract

Introduction—Late-onset Tay-Sachs disease (LOTS) is a lysosomal storage disease caused by deficient Beta-hexosaminidase A activity.

Methods—We describe a 53-year-old woman who presented with adult-onset leg weakness, and whose initial diagnosis was progressive muscular atrophy without identifiable etiology. Development of cerebellar ataxia in mid-life prompted reassessment.

Results—Beta-hexosaminidase A quantification assay demonstrated absence of the isozyme. Genetic testing identified compound heterozygous mutations in the *HEXA* gene, confirming the diagnosis of LOTS.

Conclusions—The phenotypic spectrum of LOTS includes motor neuronopathy, ataxia, choreoathetosis, neuropathy, and psychiatric symptoms in various combinations. This patient highlights the emergence of different clinical features over many years and emphasizes the need to consider LOTS in the differential diagnosis of progressive muscular atrophy.

Keywords

late-onset Tay-Sachs disease; hexosaminidase; progressive muscular atrophy; ataxia; cerebellum

Late-onset Tay-Sachs disease (LOTS) is an autosomal recessive lysosomal storage disease due to compound heterozygous or homozygous mutations in *HEXA*.[1] These lead to decreased Beta-hexosaminidase A activity and subsequent intracellular accumulation of CNS gangliosides.[2] Patients may present in childhood, adolescence, or early adulthood. Initial features may include weakness due to motor neuron disease, neuropathy, dysarthria, spasticity, dystonia, tremor, ataxia or psychosis.[3] We present a woman who was first seen by us at age 53 with a diagnosis of spinal muscular atrophy (SMA) which had been symptomatic since her 20s. The emergence of additional features suggested the involvement of central systems and prompted diagnostic reevaluation.

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CASE REPORT

This 53-year-old woman had leg cramps and difficulty running since childhood but was otherwise in excellent health until her early 20s when she had difficulty arising from a chair and stepping from a curb. At age 28 she developed difficulty climbing stairs and a wide-based, waddling gait, prompting her first neurological evaluation. She was of Ashkenazi Jewish descent and did not have a family history of weakness or gait disorder. There was no known consanguinity. Records from her evaluation at age 28 reported symmetric proximal arm and leg weakness. Electrodiagnostic studies (EDX) suggested “chronic neuropathy,” but further details were unavailable. Muscle biopsy revealed nonspecific changes, including a preponderance of type I fibers with increased oxidative activity in the subsarcolemmal region in many fibers and a slight increase in interfascicular connective tissue. Brain MRI was reportedly unremarkable.

In her mid-30s, climbing stairs and standing from a chair became more difficult, and she began to fall every few months. There was no myalgia or muscle atrophy. Repeat EDX presumably indicated motor neuron disease (although a formal report was not available), and the possibility of a variant of SMA was raised. Genetic testing was not pursued.

In her early 40s she developed intermittent hand tremor and decreased dexterity, which affected her handwriting. Speech became slurred and had a staccato quality. By her late 40s, balance problems led to falls and injuries, and by age 51 she used a walker intermittently.

She was reevaluated by a neurologist at age 52. Brain MRI now showed isolated, prominent cerebellar atrophy (Fig. 1), and EDX were reported as consistent with “chronic, generalized motor axonopathy.” Comprehensive spinocerebellar ataxia (SCA) and recessive ataxia panels revealed no mutations in the genes coding for SCAs 1, 2, 3, 5, 6, 7, 8, 10, 12, 13, 14, 17, 28 or dentatorubral-pallidoluysian atrophy, nor in the *FXN*, *APTX*, *SETX*, *POLG1*, *SIL1*, or *TTPA* genes.

We first evaluated her at age 53. Cognition was excellent, and she had monotonic but pressured and fluent speech. Her extraocular movements were full in all directions, with normal saccades, optokinetic nystagmus, and no square wave jerks. Other cranial nerve functions were normal. Triceps, iliopsoas, and quadriceps muscle strength was graded as 4-/5 bilaterally, and other muscles demonstrated full strength. Tone was normal. Reflexes were 3+ in the arms and 1+ in the legs with no Babinski signs. Gowers sign was present. Occasional mild chorea was seen, mostly in the form of fidgetiness while seated, although some subtle upper trunk movements were also present. A mild amplitude, medium frequency finger tremor was evident bilaterally when performing the finger-nose-finger maneuver. There was no bradykinesia, although rapid alternating movements were clumsy. Sensation was normal for pinprick, temperature, vibration, and position. There was overshoot and dysmetria in the arms and legs. The gait was ataxic and wide-based, there were slow, cautious turns, and she used a walker. She was unable to tandem walk and had poor postural stability.

Vitamin E levels and thyroid function tests were normal. While total hexosaminidase quantification was normal (13.6 U/L, reference range 10.4–23.8), hexosaminidase A activity

was absent. Genetic testing identified the TATCins1278 and Gly269Ser Tay-Sachs disease mutations. Of note, the latter is known to be associated with LOTS in the homozygous state, or in compound heterozygosity with a null allele.[1] Null alleles are associated with the classic, acute infantile variant of Tay-Sachs disease when present in the homozygous state.

DISCUSSION

The differential diagnosis of progressive muscular atrophy (PMA) beginning as cramping and difficulty running in childhood includes both hereditary and sporadic childhood onset disorders.[3] Juvenile-onset progressive weakness and motor neuronopathy may be due to SMA types III or IV,[4] juvenile-onset amyotrophic lateral sclerosis (ALS),[3] the GM2 gangliosidoses, and Fazio-Londe syndrome. The exclusively proximal pattern of weakness present in the patient is not particularly suggestive of Fazio-Londe syndrome[5] or a juvenile form of ALS but is observed in SMA variants and GM2 gangliosidoses. Hence, assessing hexosaminidase levels would have been justified at the time of initial presentation.

The late onset of tremor, decreased dexterity, speech changes, and frequent falls suggested cerebellar pathology, which was likely either absent or very subtle at the time of initial evaluation. The presence of ataxia suggests an SCA or an autosomal recessive ataxia as an additional consideration. Although cerebellar atrophy would be expected as a feature in either of these conditions, it is possible that it was not prominent early in the course of her disease. Some SCAs, as well as autosomal recessive ataxias, may overlap with motor neuron disease: SCA 2 may present with progressive ataxia, parkinsonism and motor neuropathy[6]; SCA 3 typically affects the cerebellar, pyramidal, extrapyramidal, motor neuron, and oculomotor systems[7]; SCA 36 may show adult-onset truncal and limb ataxia, dysarthric ataxia, hyperreflexia, fasciculations, and atrophy[8]; and in SCAR8 upper and lower motor involvement may precede the development of cerebellar ataxia[9] by years.[10] Of interest, ataxia-telangiectasia may include pure distal SMA in the absence of ataxia.[11]

As with PMA, the differential for cerebellar ataxia also includes GM2 gangliosidoses, particularly if patients belong to an ethnic group in which the mutation carrier state is known to be highly prevalent. The GM2 gangliosidoses include Sandh-off and Tay-Sachs disease, and the former is caused by mutations in the *HEXB* gene.[2,12] Patients with late-onset Sandhoff disease usually present with either a cerebellar syndrome or lower motor neuron disease, and a few show isolated autonomic dysfunction.[12] Neuronopathy and axonopathy that are either mild or only detectable by EDX have also been reported.[12]

Given the patient's ethnic background, the preferential weakness of the triceps and quadriceps muscles, and the presence of tremor and subtle chorea, LOTS is the more likely clinical diagnosis, as was determined by enzyme assessment and further confirmed by genetic testing. The isolated cerebellar atrophy on MRI and generalized motor axonopathy on EDX are also consistent with the diagnosis. The initial presentation of motor neuron disease followed years later by cerebellar ataxia attests to the phenotypic progression that may be seen in individuals throughout their lifetimes. It is not clear when the tremor and chorea began, as they were undoubtedly mild initially.

Although the phenotypic spectrum of the disease has been well characterized, atypical presentations have been described in patients with LOTS. Shapiro and Natowicz reported a case of childhood stutter that was later identified as LOTS.[13] In 8 of a cohort of 30 patients with LOTS, Shapiro et al. also found evidence of a predominantly axonal polyneuropathy affecting distal nerve segments in the arms and legs.[14] Godeiro-Junior et al. chronicled a 30-year-old Brazilian Caucasian man with young onset and slowly progressive spastic tetraparesis resembling primary lateral sclerosis whose brain MRI revealed abnormal signal in the corticospinal tracts, as seen in typical ALS, but there was no cerebellar atrophy.[15] Hexosaminidase A quantification revealed reduced isozyme levels, but no genetic analysis was performed. Psychiatric features may also be the presenting symptom, as was reported in a boy with treatment-resistant catatonic schizophrenia who rapidly developed neuroleptic malignant syndrome after being exposed to neuroleptics[16] and whose metabolic screening revealed a severe hexosaminidase A deficiency.

Although infantile Tay-Sachs disease is lethal, the prognosis is more variable in LOTS, making its accurate diagnosis important for different reasons. First, and as mentioned above, certain psychotropic medications (particularly haloperidol, chlorpromazine, and risperidone) may worsen the neurologic condition of patients with LOTS and should be avoided.[2,16] Furthermore, while clinical trials, such as substrate deprivation therapy with miglustat[17] or enzymatic rescue with pyrimethamine,[18] did not demonstrate efficacy, there remains great promise for treatment of slowly evolving metabolic diseases such as LOTS. While our patient was of Ashkenazi descent and the mutation readily identified as confirmatory, in other populations, screening for the common mutations may be insufficient. Thus, measurement of enzyme activity should be performed as an initial step when the diagnosis is suspected. Finally, because LOTS manifests in compound heterozygotes, awareness of the carrier state has important implications in selected populations where the prevalence of infantile Tay-Sachs is known to be high. In LOTS, patients harbor 1 childhood onset mutation and 1 adult-onset mutation,[1] and unless the adult-onset mutation is included in the screening, the risk for LOTS transmission may not be known. Therefore, family members of LOTS patients with identified mutations should have the adult-onset mutations included in their prenatal screen to ensure accurate genetic counseling.

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Abbreviations

AOA2	ataxia-oculomotor apraxia 2
ALS	amyotrophic lateral sclerosis

EDX	electrodiagnostic studies
HEXA	gene coding for the α subunit of hexosaminidase
HEXB	gene coding for the β subunit of hexosaminidase
LOTS	late-onset Tay-Sachs
PMA	progressive muscular atrophy
SCAs	spinocerebellar ataxias
SETX	senataxin
SMA	Spinal muscular atrophy

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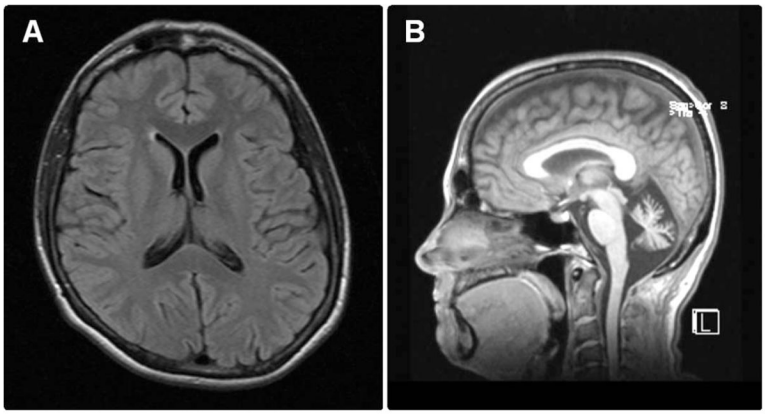

FIGURE 1.

Brain MRI, age 52. Axial T2-weighted **(A)** and sagittal **(B)** T1-weighted brain MRI shows marked prominence of the cerebellar and vermian sulci with enlargement of the 4th ventricle consistent with cerebellar volume loss. Notice the normal appearance of the brainstem and the supratentorial ventricles, sulci, and brain parenchyma.