Journal of Neurology (2019) 266:1953–1959
https://doi.org/10.1007/s00415-019-09364-3

ORIGINAL COMMUNICATION

Amyotrophy, cerebellar impairment and psychiatric disease are the main symptoms in a cohort of 14 Czech patients with the late-onset form of Tay–Sachs disease

Helena Jahnová[1] · Helena Poupětová[1] · Jitka Jirečková[1] · Hana Vlášková[1] · Eva Košťálová[1] · Radim Mazanec[3] · Alena Zumrová[4] · Petr Mečíř[2] · Zuzana Mušová[5] · Martin Magner[1]

Received: 2 December 2018 / Revised: 2 May 2019 / Accepted: 6 May 2019 / Published online: 10 May 2019

Abstract

Background Tay–Sachs disease (TSD) is an inherited neurodegenerative disorder caused by a lysosomal β-hexosaminidase A deficiency due to mutations in the *HEXA* gene. The late-onset form of disease (LOTS) is considered rare, and only a limited number of cases have been reported. The clinical course of LOTS differs substantially from classic infantile TSD.

Methods Comprehensive data from 14 Czech patients with LOTS were collated, including results of enzyme assays and genetic analyses.

Results 14 patients (9 females, 5 males) with LOTS were diagnosed between 2002 and 2018 in the Czech Republic (a calculated birth prevalence of 1 per 325,175 live births). The median age of first symptoms was 21 years (range 10–33 years), and the median diagnostic delay was 10.5 years (range 0–29 years). The main clinical symptoms at the time of manifestation were stammering or slurred speech, proximal weakness of the lower extremities due to anterior horn cell neuronopathy, signs of neo- and paleocerebellar dysfunction and/or psychiatric disorders. Cerebellar atrophy detected through brain MRI was a common finding. Residual enzyme activity was 1.8–4.1% of controls. All patients carried the typical LOTS-associated c.805G>A (p.Gly269Ser) mutation on at least one allele, while a novel point mutation, c.754C>T (p.Arg252Cys) was found in two siblings.

Conclusion LOTS seems to be an underdiagnosed cause of progressive distal motor neuron disease, with variably expressed cerebellar impairment and psychiatric symptomatology in our group of adolescent and adult patients. The enzyme assay of β-hexosaminidase A in serum/plasma is a rapid and reliable tool to verify clinical suspicions.

Keywords Late-onset Tay–Sachs disease · GM2 gangliosidosis · β-Hexosaminidase A · Ataxia · Cerebellum · Proximal weakness of lower extremities

Introduction

Tay–Sachs disease (TSD, OMIM 272800, 606869) is one of three neurodegenerative disorders caused by the intralysosomal storage of a specific glycosphingolipid, GM2 ganglioside, in neurons. Physiologically, the degradation of GM2 ganglioside is performed by the intralysosomal enzymes β-hexosaminidase A (HexA) and β-hexosaminidase B (HexB) in cooperation with a specific glycoprotein called GM2 activator. Both HexA and HexB are dimers. HexA is

✉ Martin Magner
martin.magner@vfn.cz

[1] Department of Paediatrics and Adolescent Medicine, First Faculty of Medicine, Charles University and General University Hospital in Prague, Ke Karlovu 2, 120 00 Prague 2, Czech Republic

[2] Department of Neurology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

[3] Department of Neurology, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic

[4] Department of Paediatric Neurology, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic

[5] Department of Biology and Medical Genetics, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic

a heterodimer composed of subunit α, the product of the *HEXA* gene, and subunit β, the product of the *HEXB* gene. HexB is a homodimer containing two β subunits. TSD (the B variant of GM2 gangliosidosis) is characterized by very low or absent HexA activity in the serum, plasma, dried blood spot, white blood cells or other tissues from a symptomatic person in the presence of normal or elevated HexB activity. Mutations specific for TSD are present in the *HEXA* gene. Significantly decreased or absent activities of both HexA and HexB are typical for Sandhoff disease (the 0 variant of GM2 gangliosidosis), with associated mutations in the *HEXB* gene. In the very rare disorder GM2 activator deficiency (the AB variant of GM2 gangliosidosis), the enzyme activities of both HexA and HexB are normal with fluorogenic substrates [1, 2]. All three disorders have autosomal recessive inheritance.

TSD is classified into three subtypes according to the clinical course—an acute infantile (classic) form with rapid progression and death before the age of 4 years, a subacute juvenile form with onset in early childhood and longer survival, and a chronic adult/late-onset form (LOTS) with slow progression and long-term survival. While the infantile form is characterized by early and rapid neurodevelopmental regression, epileptic seizures and vision deterioration with a typical "cherry-red spot" caused by the accumulation of various sphingolipids within retinal cells [3], the main reported symptoms of LOTS are cerebellar and extrapyramidal signs, lower motor neurons impairment and variable psychiatric conditions [2].

The birth prevalence of the acute infantile form of TSD was originally very high in the Ashkenazi Jewish community (approximately 1:3600) and some other genetically isolated populations. The introduction of population-based carrier screening, education and counselling helped to decrease the frequency of infantile TSD patients in such endangered communities [4-6]. On the other hand, LOTS, which is not so tightly associated with the Ashkenazi Jewish community, has rarely been reported in the literature. A study of 21 patients with LOTS was published in the USA [7], but only 3 isolated case reports have been published in Europe [8-10]. A substantial number of LOTS patients may escape a correct diagnosis, as their clinical symptomatology significantly differs from the well-known picture of classic infantile TSD [7, 11]. Although an effective treatment for TSD is not available at present, evaluation of the occurrence and clinical manifestation of LOTS may be important for future progress in this field. Therefore, we present clinical phenotypes, laboratory data and mutation spectrums of 14 Czech patients with LOTS, diagnosed between the years 2002 and 2018.

Patients and methods

Patients

In all patients, final diagnoses of LOTS were performed in the Department of Paediatrics and former Institute of Inherited Metabolic Disorders of the First Faculty of Medicine, Charles University in Prague. Two patients were primarily revealed by clinical exome sequencing (CES) in the molecular genetic laboratory of the Department of Biology and Medical Genetics of the Second Faculty of Medicine, Charles University and University Hospital Motol in Prague. Brain MRI and electromyography/nerve conduction velocity (EMG/NCV) studies were conducted through neurologists who provided regular patient care. Clinical examinations were carried out by clinicians of the concerned institution in cooperation with individual patients' neurologists. To our knowledge, the reported 14 patients represent the absolute majority of Czech patients diagnosed with LOTS in the past 20 years.

Enzymology

For the determination of enzyme activities, serum, plasma and white blood cells were prepared by standard procedures. The activities of the lysosomal enzymes β-hexosaminidase A (*N*-acetyl-β-D-glucosaminidase A) and β-D-galactosidase (control enzyme) were determined by fluorometric methods using 4-methylumbelliferyl-6-sulpho-2-acetamido-2deoxy-β-D-glucopyranoside and 4-MU-β-D-galactopyranoside as substrates, respectively [12].

Molecular genetic analyses

Genomic DNA was isolated from blood. Mutation analysis in all but two patients was based on direct sequencing of PCR products for all coding exons (1 to 14) of the *HEXA* gene using a 3500xL Genetic Analyzer capillary sequencer (Applied Biosystems). Primer specifics and reaction conditions are available upon request. The DNA mutations are described according to actual *HEXA* reference DNA sequence [13] (nomenclature via HGVS recommendations) [14]. For the CES of two patients, a Focused Exome and SureSelect Reagent kit (Agilent Technologies) was used for clinical exome capture, and sequencing was performed with an Illumina HiSeq1500 system. The detected variants were confirmed by Sanger sequencing.

Ethics

All information were accessed in accordance with the applicable laws and ethical requirements for the study period concerned (in particular the Helsinki Declaration, revised in 2000). All patients signed informed consent with genetic testing. The study was approved by the Institutional Review Board of the General University Hospital in Prague (Ethics Committee Approval Number: 41/12).

Results

Study group

In total, 14 LOTS patients from 10 families, 9 females and 5 males, were included in the study (Table 1). All but one were diagnosed between the years 2011 and 2018. The median age of first symptoms was 21 (range 10–33 years), while the median age of the diagnostic assessment was 35 years (range 18–54 years), resulting in a median diagnostic delay of 10.5 (range 0–29 years). The calculated birth prevalence of LOTS for the Czech Republic (CR) is 1 per 325,175 live births and the calculated birth prevalence of all forms of TSD in the CR is 1 per 212,071 live births. No patient reported was of Jewish Ashkenazi ancestry. All but one patient are still alive; the first diagnosed patient (Table 1, Pt 6) died due to complications from a head injury.

Clinical manifestations

The main clinical findings are summarized in the Table 1 (initial complaints) and Table 2 (neuropsychiatric symptomatology).

Table 1 Onset of the disease, enzyme activity and mutations in the *HEXA* gene in 14 Czech patients with the late-onset form of Tay–Sachs disease

No	*G*	Age at onset (years)	First symptoms	Age at diagnosis (years)	Diagnostic delay (years)	Approx. Resid. Enzyme activity in L (%)	Mutations (gene *HEXA*), predicted effect on protein
1[a]	F	10	Slurred speech	30	20	2.2	c.805G>A/c.1123delG p.G269S/p.E375Rfs*7
2[a]	F	15	Slurred speech, proximal weakness (LE)	18	3	2.5	c.805G>A/c.1123delG p.G269S/p.E375Rfs*7
3	M	30	Cerebellar ataxia, falls, dysmetria, dysarthria	46	16	2.3	c.805G>A/c.1073 + 1G>A p.G269S/missplicing
4[a]	F	30	Depression, proximal weakness (LE), dysphonia	38	8	3.3	c.805G>A/c.1274_1277dupTATC p.G269S/p.Y427Ifs*5
5[a]	F	30	Depression, proximal weakness (LE), dysarthria	33	3	3.7	c.805G>A/c.1274_1277dupTATC p.G269S/p.Y427Ifs*5
6	M	18	Schizophrenia-like disorder	31	13	4.1	c.805G>A/c.806G>A p.G269S/p.G269D
7	M	33	Tremor, cerebellar ataxia, dysarthria	37	4	1.8	c.805G>A/c.805G>A p.G269S/p.G269S
8	F	20	Cerebellar ataxia, tremor, proximal weakness	45	25	2.4	c.805G>A/c.1274_1277dupTATC p.G296S/p.Y427Ifs*5
9	F	23	Cerebellar ataxia, proximal weakness (LE), tremor (UE)	38	15	2.6	c.805G>A/c.1123delG p.G269S/p.E375Rfs*7
10[a]	M	25	Proximal weakness (LE), falls, slurred speech	46	21	3.8	c.805G>A/c.754C>Tb p.G269S/p.R252Cb
11[a]	M	25	Proximal weakness (LE), slurred speech	54	29	3.5	c.805G>A/c.754C>Tb p.G269S/p.R252Cb
12[a]	F	17	Mild dysarthria, proximal weakness (LE), falls	24	7	3.3	c.805G>A/c.1274_1277dupTATC p.G296S/p.Y427Ifs*5
13[a]	F	17	Proximal weakness (LE), falls	20	3	3.7	c.805G>A/c.1274_1277dupTATC p.G296S/p.Y427Ifs*5
14	F	25	Dysarthria, proximal weakness (LE), tremor (UE)	25	0	2.9	c.805G>A/c.1073 + 1G>A p.G296S/missplicing

LE low extremities, *UE* upper extremities, *L* leukocytes, *F* female, *M* male

[a]Patients 1 and 2; 4 and 5; 10 and 11; 12 and 13 are siblings

[b]Mutation in siblings 10 and 11 is novel

Table 2 Neuropsychiatric symptomatology in the group of 14 Czech patients with late-onset form of Tay–Sachs disease

No.	Weakness and amyotrophy of LE	Anterior horn cells neuronopathy (based on EMG/NCV and clinical findings)	Dysmetria, action tremor of UE (neocerebellar syndrome)	Slurred speech, stammering, dysarthria	Cerebellar ataxia, gait instability (paleocerebellar syndrome)	Dystonia, dyskinesia	Pyramidal signs	Psychosis	Mild cognitive impairment	Cerebellar atrophy (MRI)
1	+	+	+	+	+	−	−	+	−	+
2	+	+	+	+	+	−	−	−	−	+
3	−	ND	+	+	+	−	−	−	−	+
4	+	+	−	+	−	+	−	+	+	+
5	+	+	−	+	−	+	−	+	+	+
6	−	ND	+	−	+	−	−	+	−	+
7	+	+	+	+	+	−	−	−	−	+
8	+	+	+	−	+	−	−	+	−	+
9	+	+	+	−	+	−	−	−	+	+
10	+	+	−	+	+	−	−	−	−	+
11	+	+	−	+	+	−	−	−	−	+
12	+	+	+	+	+	−	−	−	+	+
13	+	+	−	−	+	−	−	−	−	+
14	+	+	+	+	−	−	−	−	−	+

N number, *LE* lower extremities, *UE* upper extremities, *MRI* magnetic resonance imaging, *EMG* electromyography, *NCV* nerve conduction velocity, *ND* not done

Generally, the main initial complaints in the cohort were mild articulation difficulties, especially slurred rapid speech and/or stammering (nine patients), proximal weakness of the lower extremities limiting walking down and up the stairs (nine patients), dysmetria, action tremor and gait instability with frequent falls (eight patients), and/or schizophrenic and maniodepressive disorders (three patients). Some patients reported having been "a clumsy child", but others (three patients) participated in various sports during childhood and adolescence. No optic atrophy or "cherry-red spot" was described in any patient, but mild variable signs of oculomotoric dysfunction (gaze dyscoordination, mild saccade and pursuit irregularity) were present in some patients during clinical progression of the disease. Fluctuating horizontal nystagmus was present in one male (Pt 7). Some patients suffered from common myopia or hypermetropia. In one male (Pt 3), gait instability with frequent falls and severe dysmetria without significant weakness of the lower extremities (combined cerebellar syndrome) dominated. He had no nystagmus, nor any other ocular movement dysfunction. Organomegaly and/or cardiac disease were not found in any patient of the cohort.

In three patients, the first symptom of LOTS was a psychiatric disorder. In one male (Pt 6), acute schizophrenia-like disorder with relapses preceded the development of combined cerebellar symptomatology by 6 years. Schizoaffective disorder (predominantly depression) and weakness of the lower extremities were the first symptoms in two sisters (Pts 4 and 5). In another two females (Pts 1 and 8), severe episodes of maniodepressive disorder requiring psychopharmacologic treatment appeared about 10 years after manifestation of the first motor symptoms. Four other patients suffered from likely secondary moderate depressive symptomatology. All but one patient underwent at least one psychological examination; mild cognitive decline was assessed in four females, while in other patients, the overall cognitive level was normally distributed.

Mild dystonia/dyskinesia in two females (Pts 4 and 5) may have been partly due to neuroleptic treatment. No signs of pyramidal tract impairment were found in patients of the cohort.

In patients manifesting predominantly with proximal weakness of the lower extremities, results of complex neurological examinations corresponded to anterior horn cell damage. These patients had proximal and distal amyotrophy predominantly in the lower limbs without any sensory impairment. Fasciculations were noticed only rarely in some patients, less frequently in severely disabled persons. EMG/NCV studies were performed in 12 patients and documented chronic neurogenic lesion with reinnervation changes of motor unit potentials (MUPs), especially in the proximal muscles of lower extremities, corresponding to anterior horn cell neuronopathy.

Variably prominent lamellar cerebellar atrophy (in two females very mild) was found in brain MRI in all 14 patients.

Laboratory findings

Residual enzyme activities ranged between 1.8 and 4.1% of the control average; there were no significant differences in serum/plasma and leukocytes. The most frequent nucleotide expansion-based spinocerebellar ataxias (SCAs) were excluded by routine DNA analyses in six patients. Due to the clinical picture resembling spinal amyotrophy, DNA analysis of the *SMN1* gene was performed in ten patients with normal results, while the late-onset form of Pompe disease was excluded in five patients by an enzyme assay. The c.805G>A (p.Gly269Ser) mutation that is typically associated with LOTS [9] was found in all 14 patients, with 1 patient carrying this mutation on both alleles (Table 1, Fig. 1). In half of cases (7/14), a compound heterozygosity for c.805G>A and the previously described null mutation (c.1073+1G>A or c.1274_1277dup) were detected, while in another three cases, the c.805G>A mutation occurred along with the frameshift mutation c.1123delG. The remaining two patients were carriers of a previously unpublished missense mutation c.754C>T (p.Arg252Cys). One patient carried the mutation c.806G>A, which is the first nucleotide of exon 8 in the conserved splice domain (possibly inducing missplicing).

Discussion

LOTS is considered to be a very rare disease. However, in the Czech Republic, with 10.58 million inhabitants, 13 patients have been diagnosed in the last 8 years, which is in sharp contrast to only 3 isolated cases published by European authors so far [8-10]. From the genetic point of view, it is likely that the Czech population does not differ from other European countries substantially. We presume

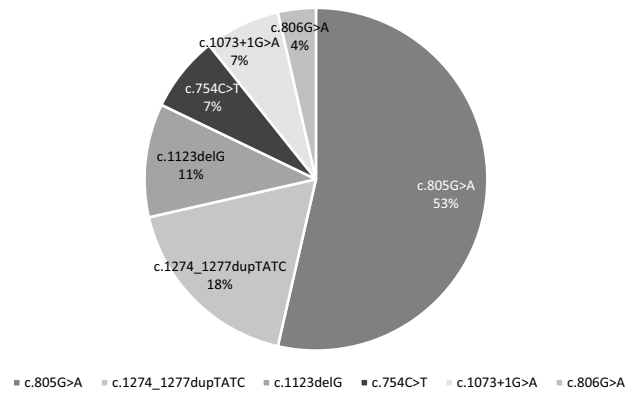

Fig. 1 Frequency of distinct mutations in the group of 14 Czech patients with the late-onset form of Tay–Sachs disease

that reasons for the apparent underdiagnosis of this disease, documented also by the long interval between age of onset and age of diagnosis, include both the quite different clinical symptomatology of LOTS in comparison with the infantile form TSD and the broad differential diagnostic spectrum of spinal muscular atrophy, motor axonal neuropathies, cerebellar disorders and psychiatric conditions.

Neurological clinical features of LOTS are variable, but slowly progressing symptoms of anterior horn cell neuronopathy especially at the lower extremities and cerebellar dysfunction (not necessarily simultaneously in one patient) are prominent. In accordance with literary sources, about half of patients in our cohort suffered from psychiatric disturbances including schizophrenia-like psychosis and depression, and in three persons these symptoms represented the first manifestation of LOTS. Psychiatric symptoms were sometimes atypical and bizarre, such as disorganized schizophrenia, catatonia, regression to childhood behaviour or conflicting personality disorder (as in Pt 6) [15, 16].

While amyotrophy of the lower limbs and cerebellar signs (dysmetria, action tremor, severe gait instability without sensory deficits, typical dysarthria) were frequent symptoms in our patients with LOTS, dystonia mentioned in the literature was found in only two females of our cohort. A partial effect of neuroleptic treatment could not be excluded. It is important to mention that falling in LOTS is often the result of "knee buckling" due to weakness of knee extensor muscles rather than due to ataxia. Only four of our patients suffered from mild cognitive impairment, though the possibility of a negative influence from reactive depression is not negligible. The absence of significant cognitive decline or dementia in our patients is in concordance with findings in a group of 21 American patients, and thus seems to be an important feature of LOTS [7]. The involvement of the eyes in some patients was minimal and unspecific. There was no optic nerve atrophy or finding of a “cherry-red spot” in our cohort. EMG/NCV findings indicating chronic anterior horn cell neuropathy and cerebellar atrophy in the brain MRI were typical clinical laboratory findings.

Based on our experience, the enzyme assay of β-hexosaminidase A in serum/plasma is a rapid, inexpensive and reliable tool to verify clinical suspicion, and we did not experience any false positive result in our Czech cohort. Similarly as in some other lysosomal disorders, β-hexosaminidase A activity assessment in serum/plasma/dried blood spot could serve as a possible screening method in the groups of clinically selected patients.

In line with literary data [17], the presence of the p.Gly269Ser (c.805G>A) allele in the *HEXA* gene responsible for incorrect enzyme dimer forming is typical for the adult form of the disease. Combinations with null alleles in our group of patients led to both a more complex symptomatology and a more progressive course of disease. In two brothers with the common c.805G>A mutation and the novel c.754C>T mutation, LOTS manifested in their 3rd decade, but the course was slow, with relatively mild weakness of the lower extremities, mild cerebellar symptomatology and normal cognitive functions.

Currently, there is no effective treatment for LOTS and management is only supportive, but several treatment strategies have been tested. Although bone marrow transplantation led to stabilisation of the disease in a 15-year-old boy [18], the therapeutic effect is generally considered to be minimal [19]. Intrathecal infusion of the pure β-hexosaminidase A was tested in two patients with the infantile form TSD with no benefit [20]. Substrate reduction therapy with miglustat or chaperone therapy with pyrimethamine likewise showed no clinical benefits [21, 22]. While the results of these studies are still not satisfactory, we strongly believe that a higher number of diagnosed patients may enhance research for effective treatment.

Conclusion

Though the individual clinical course of disease is variable, the combination of slowly progressive anterior horn cell neuronopathy manifesting mostly at the lower extremities, with variably expressed cerebellar symptomatology and corresponding cerebellar atrophy in the brain MRI should direct clinicians´ suspicion to LOTS, especially if episodes of psychotic behaviour occur simultaneously. A serum/plasma enzyme assay of beta-hexosaminidase A activity is an inexpensive and reliable primary diagnostic tool. We hope that the increased number of diagnosed patients will support efforts in the search for effective treatments.

Acknowledgements The work was supported by the Grant UNCE 204064; PROGRES Q26/LF1 and RVO-VFN 64165/2012.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Gravel RA, Kaback MM, Proia RL, et al (2014) The GM2 Gangliosidoses. In: The online metabolic and molecular bases of inherited diseases
2. Kaback MM, Desnick RJ (2011) Hexosaminidase A deficiency. In: Pagon R, Adam M (eds) GenReviews, pp 1993–2018
3. Chen H, Chan AY, Stone DU, Mandal NA (2014) Beyond the cherry-red spot: Ocular manifestations of sphingolipid-mediated neurodegenerative and inflammatory disorders. Surv. Ophthalmol. 59:64–76
4. Kaback M, Lim-Steele J, Dabholkar D et al (1994) Tay–Sachs disease—carrier screening, prenatal diagnosis and the molecular

era: an international perspective, 1970 to 1993. Obstet Gynecol Surv 270:2307–2315. https://doi.org/10.1097/00006254-199405000-00013
5. Kaback MM (2000) Population-based genetic screening for reproductive counseling: the Tay–Sachs disease model. Eur J Pediatr 159:192–195. https://doi.org/10.1007/PL00014401
6. Scott SA, Edelmann L, Liu L et al (2010) Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases. Hum Mutat 31:1240–1250. https://doi.org/10.1002/humu.21327
7. Neudorfer O, Pastores GM, Zeng BJ et al (2005) Late-onset Tay–Sachs disease: phenotypic characterization and genotypic correlation in 21 affected patients. Genet Med 7:119–123
8. Steiner KM, Brenck J, Goericke S, Timmann D (2016) Cerebellar atrophy and muscle weakness: late-onset Tay–Sachs disease outside Jewish populations. BMJ Case Rep 31:5
9. Barritt AW, Anderson SJ, Leigh PN, Ridha BH (2017) Late-onset Tay–Sachs disease. Pract Neurol 17:396–399. https://doi.org/10.1136/practneurol-2017-001665
10. Prihodova I, Kalincik T, Poupetova H et al (2013) Late-onset Tay–Sachs disease can mimic spinal muscular atrophy type III—two case reports. Ces a Slov Neurol a Neurochir 76:221–224
11. Navon R, Argov Z, Frisch A (1986) Hexosaminidase A deficiency in adults. Am J Med Genet 24:179–196. https://doi.org/10.1002/ajmg.1320240123
12. Wenger D, Williams C (1991) Screening for lysosomal disorders. In: Hommes FA (ed) Techniques in diagnostic human biochemical genetics. Willey-Liss, New York, pp 587–617
13. HEXA hexosaminidase subunit alpha [Homo sapiens (human)]. https://www.ncbi.nlm.nih.gov/gene/3073. Accessed 30 Sep 2018
14. Human genom variation society. https://www.hgvs.org/. Accessed 17 Sep 2018
15. Streifler J, Golomb M, Gadoth N (1989) Psychiatric features of adult GM2gangliosidosis. Br J Psychiatry 155:410–413. https://doi.org/10.1192/bjp.155.3.410
16. MacQueen GM, Rosebush PI, Mazurek MF (1998) Neuropsychiatric aspects of the adult variant of Tay–Sachs disease. J Neuropsychiatry Clin Neurosci 10:10–19. https://doi.org/10.1176/jnp.10.1.10
17. Navon R, Proia RL (1989) The mutations in Ashkenazi Jews with adult GM2gangliosidosis, the adult form of Tay–Sachs disease. Science 243:1471–1474. https://doi.org/10.1126/science.2522679
18. Stepien KM, Lum SH, Wraith JE et al (2017) Haematopoietic stem cell transplantation arrests the progression of neurodegenerative disease in late-onset Tay–Sachs disease. JIMD Rep 41:17–23. https://doi.org/10.1007/8904_2017_76
19. Neudorfer O, Kolodny EH (2004) Late-onset Tay–Sachs disease. Isr Med Assoc J 6:107–111
20. von Specht BU, Geiger B, Arnon R et al (1979) Enzyme replacement in Tay–Sachs disease. Neurology 29:848–854. https://doi.org/10.1212/WNL.29.6.848
21. Shapiro BE, Pastores GM, Gianutsos J et al (2009) Miglustat in late-onset Tay–Sachs disease: a 12-month, randomized, controlled clinical study with 24 months of extended treatment. Genet Med 11:425–433. https://doi.org/10.1097/GIM.0b013e3181a1b5c5
22. Osher E, Fattal-Valevski A, Sagie L et al (2015) Effect of cyclic, low dose pyrimethamine treatment in patients with Late Onset Tay Sachs: an open label, extended pilot study. Orphanet J Rare Dis 17:10–45. https://doi.org/10.1186/s13023-015-0260-7