Late-onset Tay-Sachs disease

Article (Accepted Version)

Late Onset Tay Sachs Disease

Andrew W Barritt[1,2]*, Stuart J Anderson[1], P Nigel Leigh[1,3] and Basil H Ridha[1]

[1]*Hurstwood Park Neurosciences Centre, Haywards Heath, West Sussex, RH16 4EX, UK*

[2]*Clinical Imaging Sciences Centre, Brighton and Sussex Medical School, Falmer, BN1 9RR, UK*

Andrew W Barritt MBBS BSc MRCP(UK)	*Neurology Registrar. ORCID 0000-0002-9723-6946*
Stuart J Anderson	*Consultant Neuropsychologist*
P Nigel Leigh	*Professor of Neurology*
Basil Ridha	*Consultant Neurologist*

*Corresponding Author

Andrew W Barritt awb@doctors.org.uk

Contributorship:

AWB performed a literature search, review of the literature and drafted the article.

SA performed a literature search, review of the literature and part-drafted the article.

PNL provided clinical expertise and critical appraisal of the article for submission.

BR provided clinical expertise and critical appraisal of the article for submission.

Word Count (excluding references): 1,600

References: 14

Conflict of Interests: None declared.

Funding: This article received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Consent: Full consent from the patient for publication has been sought.

Abstract

We discuss the assessment and differential diagnoses of a young adult Hungarian man presenting with a one-year history of progressive symmetric amyotrophic lateral sclerosis (ALS)-like syndrome involving all limbs, tremor of the arms and cerebellar atrophy. A history of subtle sporting difficulty and mild bilateral hand tremor was reported in early adolescence. This remained essentially unchanged for 20 years with no limitation of full independent functioning or academic achievement to university level. Examination at current presentation revealed florid fasciculations, predominantly proximal muscle weakness and atrophy particularly affecting triceps muscles, brisk reflexes, a coarse postural and action tremor of the arms with touch sensitive myoclonus, and a wide-based waddling gait. MRI of brain and spinal cord displayed isolated cerebellar atrophy. Formal neuropsychometric testing revealed deficits in attention, processing speed and memory. Needle EMG demonstrated widespread chronic denervation whilst nerve conduction studies revealed slightly diminished sural sensory action potentials. White cell enzymes showed markedly reduced enzymatic activity of β-Hexosaminidase A. Genetic testing confirmed the presence of two heterozygous pathogenic mutations in HEXA gene: [c.1499delT p.(Leu500fs) and c.805G>A p.(Gly269Ser)]. The very rare diagnosis of adult onset Tay Sachs disease was made.

Case History

A 35-year-old right-handed Hungarian man presented with one year's history of progressive weakness in all four limbs and tremor of the arms. He had particular difficulties walking, climbing stairs and lifting objects above the head, in addition to writing which had deteriorated considerably owing to the tremor. Mild slurring of speech had recently emerged when tired. After sustaining several falls, he began using a stick when walking outdoors six months prior to presentation. 3 stone in weight had also been lost over this time, despite preserved appetite, with a noticeable loss of muscle bulk. There was no associated pain, sensory or sphincter disturbance, difficulty swallowing or breathing, and normal mood and subjective cognition.

Aged 14 the patient had been reviewed by a neurologist regarding difficulty with vertical jumping and mild unsteadiness during sports, along with a subtle bilateral hand tremor. No specific diagnosis was made and the symptoms remained static over the next 20 years, although training to become an electrician was refused owing to the tremor. A-Level education was completed in the UK before enrolling on a Business degree in the USA but, due to funding issues, was not completed and he returned to the UK aged 23. Thereafter he worked as a carer but had recently stopped due to his deteriorating condition.

Past medical history and family history were otherwise unremarkable. He and his elder brother are products of a non-consanguineous marriage without known Jewish ancestry. His 55-year-old mother resides in Latvia but his father died young in a road traffic accident. Alcohol consumption had always been minimal and he had never smoked.

On examination, the cranial nerves, including fundoscopy, were unremarkable except for mild bilateral upper motor neuron pattern facial weakness and positive pout reflexes. Neck flexion and

extension were normal. The upper limbs revealed generalised loss of muscle bulk, most markedly of triceps bilaterally, with florid fasciculations most visible in pectoralis and deltoid muscles. A coarse, irregular tremor on posture and action was visible throughout the outstretched upper limbs with symmetrically slowed alternating movements without past pointing. Stimulus sensitive myoclonus could be elicited on touching the right hand. Muscle tone was normal whereas power revealed disproportionate elbow extension weakness (2/5), along with symmetrical weakness of shoulder abduction and external rotation, elbow flexion and the first dorsal interossei (4/5). All other muscle groups had full power including the deep finger flexors. Reflexes were symmetrically brisk including deltoid and supraspinatus jerks on both sides and a right Hoffman sign. In the lower limbs, tone was normal but there was symmetrical weakness of hip flexion (2/5), knee flexion (3/5) and knee extension (2/5), but with fully preserved hip extension. Flexion of the great toes and ankle inversion were 4/5 bilaterally with all other muscle groups having full power. Knee and ankle reflexes were symmetrically brisk with bilateral crossed adductors. Plantar responses were extensor but there was no ankle clonus. Sensory examination was entirely normal. To rise from a seated position he required use of his arms and to lock his knees in extension, before walking with a slow, wide-based and waddling gait (see supplementary videos). Cardiorespiratory, abdominal, skin, lymph node and testicular examinations were normal and there was no gynaecomastia.

Blood tests revealed mildly raised CK at 603units/L (NR 0-190). He had normal or negative full blood count, renal profile, liver and thyroid function tests, CRP, ESR, ANA, ENA, serum immunoglobulin levels, serum protein electrophoresis, anti-neuronal antibodies, anti-ganglioside antibodies, HIV, syphilis, Lyme disease and hepatitis A-C serology.

Neurophysiological assessment demonstrated normal peripheral motor and sensory conductions, apart from slightly diminished sural sensory action potentials (SAPs) on both sides. Needle EMG was abnormal with widespread chronic denervation including the tongue.

MRI of brain and whole spine showed disproportionate cerebellar atrophy but otherwise normal intracranial and cervical cord appearances (Fig. 1).

Lumbar puncture revealed normal CSF opening pressure, white cell count 2 per mm^3, red cell count 2 per mm^3, protein 376mg/L, glucose 3.6mmol/L (paired serum 5.3), normal cytological analysis and negative oligoclonal bands.

ECG showed normal sinus rhythm. CT scan with contrast of chest, abdomen and pelvis revealed no visceral abnormality.

Formal neuropsychological assessment was limited by the patient's writing difficulties. Out of 14 sub-component domains he scored within the mildly impaired range in three (visual attention/working memory and delayed verbal recall; 21.4%), mild-to-moderate range in six (auditory attention/working memory, delayed visual recall, immediate verbal recall, semantic word fluency and verbal recognition memory; 42.8%), and moderate-to severe range in two (processing speed and immediate visual recall; 14.2%). In contrast, normal range performance was noted on tests of visual perception, confrontational naming, and intellectual ability/non-verbal reasoning (21.4%). Relatively preserved recognition memory suggested difficulty of retrieval rather than encoding, while prominent deficits in attention and processing speed suggested a predominantly subcortical pattern of impairment.

Differential Diagnoses

The patient displayed progressive upper and lower motor neuronopathy without sensory involvement raising the possibility of amyotrophic lateral sclerosis. However, there were atypical features including the teenage onset of tremor and sporting difficulties, the predominantly proximal pattern of muscle weakness, disproportionate wasting and weakness of triceps muscles, the jerky upper limb tremor and myoclonus, and disproportionate cerebellar atrophy. Beyond cervical myelopathy, mimics of ALS with truly mixed motor involvement are rare.[1 2] Repeat expansions of the C9orf72 gene, causative of a spectrum of phenotypes including ALS and frontotemporal dementia (FTD), can be associated with regional cerebellar atrophy but penetrance is unusual under 35 years-of-age and features of FTD were not evident here.[3 4] Cerebellar atrophy raises the possibility of a complex form of autosomal dominant spinocerebellar ataxia, such as SCA 3 (Machado-Joseph Disease) which can be associated with pyramidal signs and anterior horn cell disease. However, the absence of extraocular movement abnormalities and extrapyramidal signs were against this diagnosis. Although normal appearing white matter on brain MRI would not exclude an adult-onset adrenoleukodystrophy, the cerebellar involvement, lack of sphincter disturbance or sensory signs and subsequently normal very long chain fatty acids levels rendered this and polyglucosan body disease unlikely. Adult onset Niemann Pick type C may present with a myriad of features including cerebellar ataxia and movement disorders although the characteristic vertical supranuclear gaze palsy was absent in our case. Nevertheless, as cerebellar atrophy does constitute a recognised feature of this and other GM2 gangliosidoses a white cell enzyme (WCE) analysis was undertaken. This showed normal total hexosaminidase activity at 1210nmol/hr/mg (NR 885-5965 and includes Hexosaminidase B activity) but a markedly low white cell β-Hexosaminidase A functioning at 10nmol/hr/mg (NR 134-700), representing only 15% normal hexosaminidase A activity (usually 62-79%). Genetic testing confirmed the presence of compound

heterogeneous pathogenic mutations with both 1499T deletion and the 805G>A substitution in the HEXA gene. A definitive diagnosis of late onset Tay-Sachs disease (LOTS) was therefore made.

Discussion

β-Hexosaminidase A is a dimeric lysosomal enzyme comprising α and β subunits encoded by the HEXA gene on Chromosome 15 and the HEXB gene on Chromosome 5, respectively, and is the only one of three isozymes which hydrolyses the ganglioside GM_2 into GM_3.[5 6] GM_2 belongs to the glycosphingolipid category of sphingolipids which are essential constituents of the lipid bilayer of cell membranes[7] and is almost exclusively found in the nervous system, particularly within grey matter.[8] Abnormal accumulation of GM_2 within lysozymes is usually precipitated by a deficiency of the β-Hexosaminidase A enzyme itself, either due to autosomal recessive gene defects in HEXA (Tay Sachs disease) or HEXB (Sandhoff disease) but may arise instead, extremely rarely, due to deficiency of its activator protein encoded by the GM2A gene.[9] The nature of each individual clinical presentation is felt to be related to the degree of residual enzyme activity.[5] Most commonly, severe homozygous mutations precipitate little or no functional enzyme activity resulting in relentless developmental regression and early death in infancy.[6] Less severe enzyme defects can delay presentation until adolescence or adulthood and produce a rather hetereogeneous disease spectrum. Even in LOTS, however, there is often a history unearthed of subtle motor difficulty in childhood.[6 7] Involvement of neuromuscular weakness, pyramidal signs and cerebellar dysfunction is usually evident, as in our case, but also encountered are neuropsychiatric disturbances (in at least a third of LOTS with some patients initially believed to have schizophrenia), extrapyramidal syndromes, dystonia, overactive bladder symptoms and cognitive decline.[6 7] The diminished sural SAPs demonstrated in our patient have been observed in a subgroup of LOTS patients with a clinically-manifest sensory neuropathy,[10] but would suggest subclinical involvement in our patient.

The nature and extent of cognitive involvement in LOTS is variable with incidence of impaired cognition ranging from 0 to 50%.[7 11-13] Deficits in executive functioning and memory are the most commonly reported. Verbal impairment has been found using computerised testing (*Neurotrax*).[11]

An association between the burden of neurological involvement and degree of cognitive dysfunction has also been reported.[13] Formal neuropsychometric testing in our patient demonstrated a predominantly subcortical pattern of cognitive impairment with prominent deficits in attention, processing speed, executive function, working memory and memory retrieval. This is consistent with neuropathological findings of relatively greater involvement of the subcortical structures and cerebellum of individuals with LOTS.[14]

Clinicians should be aware of LOTS as an extremely rare mimic of ALS associated with tremor and cerebellar atrophy. Formal psychometric testing may highlight deficits which are not suspected on clinical presentation. Delineating the extent of cognitive impairment will have an impact on multidisciplinary management which remains supportive in the absence of any clinically-effective disease modifying treatment for the Hexosaminidase deficiency syndromes. Although low dose pyrimethamine, a dihydrofolate reductase inhibitor, has been shown to mediate a small but significant increase in circulating white cell Hexosaminidase A activity in LOTS patients possessing certain mutations, the effect appears to wane and even reverse with long term exposure which can correct to baseline after a period of drug freedom.[15 16] Moreover, a small open-label study reported that 3 of 4 patients continued to deteriorate over 18 months whereas the other remained stable despite a cyclical administration schedule and regular monitoring of WCE activity.[15]

Key Points

1. Late-onset Tay Sachs (LOTS) disease and adult onset GM2 gangliosidoses are extremely rare clinical entities.
2. Adults presenting with an unusual ALS-type and cerebellar syndrome should prompt consideration of (LOTS) and testing of the white cell enzymes looking particularly for Hexosaminidase A deficiency.
3. Patients with LOTS can present with subclinical cognitive deficits that are only present on formal neuropsychometric testing and typically reflect subcortical dysfunction.
4. A longstanding history of subtle clumsiness or athletic difficulties in childhood and teenage years may be present.
5. The only clue from brain imaging may be an isolated cerebellar atrophy.

Figure 1. MR brain imaging showing diffuse cerebellar atrophy on sagittal T1 (A), axial T2 (B) and coronal T1 (C) sequences with prominence of the cerebellar folia and widening of the fissures (arrowheads).

References

1. Ghasemi M. Amyotrophic lateral sclerosis mimic syndromes. *Iran J Neurol* 2016;15(2):85-91.
2. Turner MR, Talbot K. Mimics and chameleons in motor neurone disease. *Pract Neurol* 2013;13(3):153-64.
3. Bocchetta M, Cardoso MJ, Cash DM, *et al.* Patterns of regional cerebellar atrophy in genetic frontotemporal dementia. *Neuroimage Clin* 2016;11:287-90.
4. Cooper-Knock J, Shaw PJ, Kirby J. The widening spectrum of C9ORF72-related disease; genotype/phenotype correlations and potential modifiers of clinical phenotype. *Acta Neuropathol* 2014;127(3):333-45.
5. Chen H, Chan AY, Stone DU, *et al.* Beyond the cherry-red spot: Ocular manifestations of sphingolipid-mediated neurodegenerative and inflammatory disorders. *Surv Ophthalmol* 2014;59(1):64-76.
6. Neudorfer O, Kolodny EH. Late-onset Tay-Sachs disease. *Isr Med Assoc J* 2004;6(2):107-11.
7. MacQueen GM, Rosebush PI, Mazurek MF. Neuropsychiatric aspects of the adult variant of Tay-Sachs disease. *J Neuropsychiatry Clin Neurosci* 1998;10(1):10-9.
8. Stryer L. Biosynthesis of Membrane Lipids and Steroids. *Biochemistry* W.H. Freeman & Company, 1995.
9. Neudorfer O, Pastores GM, Zeng BJ, *et al.* Late-onset Tay-Sachs disease: phenotypic characterization and genotypic correlations in 21 affected patients. *Genet Med* 2005;7(2):119-23.
10. Shapiro BE, Logigian EL, Kolodny EH, *et al.* Late-onset Tay-Sachs disease: the spectrum of peripheral neuropathy in 30 affected patients. *Muscle Nerve* 2008;38(2):1012-5.
11. Elstein D, Doniger GM, Simon E, *et al.* Neurocognitive testing in late-onset Tay-Sachs disease: a pilot study. *J Inherit Metab Dis* 2008;31(4):518-23.
12. Zaroff CM, Neudorfer O, Morrison C, *et al.* Neuropsychological assessment of patients with late onset GM2 gangliosidosis. *Neurology* 2004;62(12):2283-6.
13. Frey LC, Ringel SP, Filley CM. The natural history of cognitive dysfunction in late-onset GM2 gangliosidosis. *Arch Neurol* 2005;62(6):989-94.
14. Suzuki K. Neuropathology of late onset gangliosidoses. A review. *Dev Neurosci* 1991;13(4-5):205-10.
15. Osher E, Fattal-Valevski A, Sagie L, *et al.* Effect of cyclic, low dose pyrimethamine treatment in patients with Late Onset Tay Sachs: an open label, extended pilot study. *Orphanet J Rare Dis* 2015;10:45.