Rapidly Progressive White Matter Involvement in Early Childhood: The Expanding Phenotype of Infantile Onset Pompe?

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Abstract Glycogen accumulation in the central nervous system of patients with classical infantile onset Pompe disease (IOPD) has been a consistent finding on the few post-mortems performed. While delays in myelination and a possible reduction in processing speed have previously been noted, it has only been recently that the potential for clinically significant progressive white matter disease has been noted. The limited reports thus far published infer that in some IOPD patients, this manifests as intellectual decline in the second decade of life. We present a CRIM negative patient, immunomodulated with rituximab and methotrexate at birth, who despite an initial good clinical response to ERT, at the age of just under 4 years, presented with evolving spasticity in the lower limbs. The investigation of

which revealed progressive central nervous system involvement. Given both the earlier onset of the symptoms and consanguineous familial pedigree, extensive biochemical and genetic investigation was undertaken to ensure no alternative pathology was elucidated. In light of these findings, we review the radiology and post-mortems of previous cases and discuss the potential mechanisms that may underlie this presentation.

Introduction

Prior to the advent of enzyme replacement therapy (ERT), patients with the classical infantile onset variant of Pompe disease (IOPD), a lysosomal storage disease due to a deficiency in the enzyme acid α -glucosidase (GAA) (Hers 1963) (OMIM #232300), typically died within the first year of life (van den Hout et al. 2003). The inherent mortality has been predominately attributable to cardiorespiratory failure (Byrne et al. 2011) with both the cardiac hypertrophy and the peripheral myopathy inherent to the excessive skeletal muscle lysosomal glycogen accumulation, being the major causes of morbidity and mortality (Lim et al. 2014).

While glycogen has been demonstrated to accumulate in central neuronal tissue (Gambetti et al. 1971), even prenatally (Chen et al. 2004), its effects have thus far been apparently limited. For although an initial case series of five patients of treated with ERT suggested patients may suffer from delay in CNS myelination, or in one severe case a possible dysmyelination (Chien et al. 2006) the clinical significance of these findings has been unclear, with cognitive outcome over the first decade not overtly

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impaired, excepting a slight reduction in processing speed (Ebbink et al. 2012; Spiridigliozzi et al. 2013). Even in the two case reports with recorded white matter changes in early childhood, one was gaining clinical skills (Rohrbach et al. 2010) and while clinical decline was noted in the second case. This was related to both the expected myopathy and an additional peripheral neuropathy, rather than be central in origin (Burrow et al. 2010). Indeed, only recently have there been suggestions that IOPD patients may be at risk of a clinically significant sequelae from progressive central nervous system disease. The most prominent case thus far thus involved a 9-year-old IOPD patient whose observed intellectual decline was linked with extensive and progressive periventricular and subcortical white matter lesions (Ebbink et al. 2016). We report progressive white matter changes presenting in early childhood in a classical IOPD patient and their clinical impact, where extensive biochemical and genetic investigations have failed to show alternative causation to IOPD.

Methods

The genetic investigations were performed using a combination of Next Generation Sequencing (NGS) approaches. The first NGS analysis utilised a preselected vitamin and organic acid subpanels in an in-house panel of 226 genes involved with known metabolic pathways (Ghosh et al. 2017). Here DNA from a sample of blood was enriched by an Agilent SureSelect Custom Design target-enrichment kit (Agilent, Santa Clara, CA, USA) and sequenced with Illumina HiSeq 2500 (Illumina, Inc., San Diego, CA, USA). Subsequent sequence alignment, variant calling and annotation and filtering strategy were performed as reported previously from our laboratory (Ellingford et al. 2016). The second NGS approach was a targeted exome approach using genes selected based on both the 2015 consensus document for the definition of leukodystrophies and leukoencephalopathies (Vanderver et al. 2015) and those known to cause hereditary paraplegias (Hensiek et al. 2015). The hereditary paraplegias looked at were those with an autosomal recessive inheritance, presenting with a pure paraplegia or a complex presentation with documented leukodystrophy. As with the NGS panel the target exome used DNA derived from peripheral blood sampling which was enriched using Agilent SureSelectXT Focused Exome (Agilent, Santa Clara, CA, USA) and sequenced on the NextSeq500 (Illumina, Inc., San Diego, CA, USA). Variant calling using samtools v0.1.18, with hg19 human genome as a reference, and analysis performed using VarSeq®

(Golden Helix, Bozeman, MT, USA) to identify variants present in the genes of interest with an allele frequency <1% in control populations.

CSF glucose tetrasaccharide analysis by HPLC was performed on a sample snap frozen with liquid nitrogen at the bedside, using the methodology previously described (Prunty et al. 2015).

Patient and Results

The patient, part of an extended consanguineous family affected with IOPD, was initially noted to have hypertrophic cardiomyopathy on prenatal echo at 30 weeks' gestation. He was subsequently born spontaneously, prematurely at 33 + 4 weeks' gestation. On delivery, minimal cardiac hypertrophy was seen but no other clinical abnormalities identified. Confirmation of IOPD was via lymphocyte assay and genotyping. The later showing him to be homozygous for the familial c.2237G>A p.(Trp746*) mutation, a severe mutation (Beesley et al. 1998) associated with a CRIM Negative phenotype (Broomfield et al. 2016). Immunomodulation with four doses of rituximab (375 mg/M²) and low dose methotrexate (2 doses of 0.4 mg/kg around the first six infusions) and subcutaneous immunoglobulin support was thus initiated with the onset of Myozyme 20 mg/kg weekly at 35 weeks' gestation. This dose of Myozyme was continued weekly for the first 3 months then given alternate weeks as per national protocol. No immediate acute complications were observed, with lymphocytic reconstitution occurring at 11 months of age. Clinical progress was good with normal developmental milestones achieved over the first 3 years of life with steady walking achieved at 16 months. No anti-Myozyme IgG antibodies have ever been detected.

However, at 3 years 10 months a change in gait was noted. On examination, there was increasing tightness initially in the left, then bilaterally in dorsiflexors and ultimately tight Achilles tendons. This was associated with hyperreflexia of the ankle reflexes but no other defects in peripheral neurology with proximal lower limb power remaining good and normal knee reflexes (see Fig. 1). This progressed over the course of the next year resulting in a loss of ambulation. An increase in dysarthria was noted 6 months after the lower limb signs, however audiology, cardiac and polysomnography were still unremarkable. One year on dysphagia has developed with aspiration seen on videofluoroscopy. The latest Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV)

Fig. 1 Progression of distal spasticity in lower limb spasticity series, taken at 3 years 9 months to 4 years 4 months and 5 years

performed at 4 years 10 months, showed global severe impairment.

Given the increasingly distal lower limb spasticity, the history of prematurity and the consanguinity of the family, a central nervous system pathology was considered the most likely aetiology, possibly unrelated to the infantile onset Pompe disease. MRI brain at just over 4 years of age showed a predominately frontoparietal white matter involvement, initially mildly more extensive on the right than the left reflecting clinical symptomology. The subsequent imaging 6 months later showed progression of the changes but now included mild new bilateral involvement of the external capsules. Follow-up imaging also included single voxel MR Spectroscopy TE = 30 ms obtained from the region of the right basal ganglia and the left frontal deep white matter. Spectrum from the affected left frontal deep white matter was abnormal, with increased choline (Cho) and inositol (Ins) peaks, and reduced *N*-acetyl Aspartate peak, reflecting myelin and neuronal loss. MR Imaging findings are shown in Fig. 2.

Extensive biochemical, autoimmune and infective work up was initiated on the discovery of the white matter changes. Paired Plasma and CSF amino acids, lactates and glucose were all unremarkable as were CSF pterins, B6 and biogenic amine analysis. Similarly, acyl and plasma carnitines, plasma total homocysteine, cholesterol, plasma urate, VLCFAs, transferrin isoelectrofocusing, white cell enzymology and urinary profiling for purine and pyrimidine, bile acid, oligosaccharides and glycosaminoglycans. The only detectable biochemical abnormality was a CSF MTHF of 35 nmol/l (normal range 52–105), though plasma and red cell folate levels were within the normal range. The patient has been subsequently supplemented with oral

calcium folinate at 15 mg/day without discernible response. Glucose tetrasaccharide (Glc4) in CSF was undetectable by HPLC analysis. The infective work up showed negative plasma and CSF PCR for VZZ, HSV, enterovirus and prior JC polyomavirus (JCV) infection. Immunological work up included normal total immunoglobulin, ANA, pANCA levels with anti-phospholipid antibodies being absent. Vitamin E and copper, the biochemical causes of spasticity not already covered in the biochemical white matter screen were also found to be normal.

Initial genetic profiling concentrated on known causes of low CSF folate and showed no pathogenic variants in FOLR1, MTHFR, SLC46A1, DHFR, and indeed only two variants of unknown significance in BCKDHD and PCCA both of which could be excluded as pathogenic based on the normal biochemistry. Similarly blood mitochondrial DNA analysis for common point mutations, deletions and duplications was normal. Subsequent analysis using the targeted exome revealed eight variants of unknown significance in eight genes. For the full list of genes selected and coverage please see Appendix, all the primary leukodystrophies, as classified by a recent European consensus group (Vanderver et al. 2015), had good coverage with none of the eight variants identified are predicted to be pathogenic (Richards et al. 2015).

Discussion

The case is the youngest treated IOPD patient who has demonstrated centrally mediated neurological regression. Given the consanguineous background, extensive investigation was attempted to ensure no secondary disease was

Fig. 2 MRI brain and MR spectroscopy findings. First row: initial MRI brain at 4 years. Five axial T2 images from the level of the internal capsules to the level of the centrum semiovale, and a coronal FLAIR image through the corona radiata. These demonstrate bilateral white matter changes with frontoparietal predominance involving the periventricular, deep and subcortical white matter with sparing of the U-fibres and internal capsules. In the lower row, the corresponding images to first row are displayed taken at 4 years 7 months. These demonstrate the progression of the white matter changes, which now

also includes new mild bilateral involvement of the external capsules. The single voxel MR spectroscopy at the age of 4 years 7 month, on the left obtained from the right basal ganglia, and on the right from the affected left frontal deep white matter. Apart from an increased Myoinositol (Ins) peak, the main metabolites spectrum from the right basal ganglia is within normal limits for the patient's age. The spectrum from the affected left frontal deep white matter is abnormal with increased Choline (Cho) and Ins peaks, and reduced NAA peak, reflecting myelin and neuronal loss

present, both to rule out a second treatable pathology and or identify potential targets for wider family screening. The only abnormal biochemical finding was a low CSF folate, though the level was not suggestive of a primary disorder of folate metabolism. Indeed, the subsequent sequencing of the genes involved in folate metabolism failed to show primary defect nor were any mitochondrial DNA point mutations, duplications or deletions defined in blood. The level of the folate was not suggestive of a primary defect and may well, given the extensive pathological cascades established in Pompe, reflect ongoing oxidative stress (Aylett et al. 2013). The likelihood of the leukodystrophy being driven by a reduction in CSF Methyltetrahydrofolate levels is further reduced by the lack of response to calcium folinate supplementation. There were no obvious infective or immunological triggers seen with JCV infection

specifically investigated, given its known association with progressive multifocal leukoencephalopathy post rituximab utilisation (Jelicic et al. 2015).

The lack of an alternative diagnosis despite extensive the biochemical and genetic work up would support the inference that, the progressive white matter disease was secondary to the patient's IOPD. Radiological comparison of this case to those previously documented would also seem to support this supposition. In total, there are currently eight reported IOPD patients on ERT with MRI changes (Burrow et al. 2010; Chien et al. 2006; Ebbink et al. 2016; Rohrbach et al. 2010). The radiology in these cases is very similar to this case, with all patients showing a periventricular white matter involvement with apparent sparing of the U fibres. Given the extent of the white matter disease in this patient, it was somewhat surprising to see sparing of

the internal capsule, however myelination was observed in the internal capsule in all five of the case series of Chien et al., albeit at a slightly later age than expected (Chien et al. 2006). In the oldest patient, there was again periventricular involvement and subcortical white matter involvement with subcortical predominance (Ebbink et al. 2016). Both the Ebbink et al. case and the patient here had involvement of the corticospinal tracts including the internal capsule, though Ebbink et al. reported no overt clinical sequelae unlike this case.

Mechanistically the potential for central neurological involvement in IOPD has been frequently postulated (Burrow et al. 2010; Chen et al. 2004; Rohrbach et al. 2010). Historical autopsies clearly demonstrate the presence of widespread glycogen deposition in the brain (Gambetti et al. 1971; Mancall et al. 1965; Martin et al. 1973; Shotelersuk et al. 2002). Typically, the autopsies show greatest neuronal glycogen accumulation in the cranial motor nuclei and cerebellar nuclei (Mancall et al. 1965; Martin et al. 1973) with minimal build up in the cerebral cortex (Mancall et al. 1965; Martin et al. 1973; Teng et al. 2004). However, despite limited glycogen deposition in the cortex, past autopsies have shown both neuronal loss (Mancall et al. 1965) and extensive gliosis. Indeed, in IOPD autopsies glial cell accumulation appears to be greatest in the white matter (Gambetti et al. 1971; Martin et al. 1973). This process of neuronal loss and gliosis would be supported by the spectroscopic findings in this case and the limited previous spectroscopic data (Burrow et al. 2010; Chien et al. 2006) where low NAA/creatinine ratios, suggesting neuronal loss, and raised Choline/creatinine ratio indicative of either demyelination or gliosis have been noted.

Given their pivotal role in CNS myelination (Bercury and Macklin 2015), it is always important to consider the role of oligodendrocytes in any white matter abnormality, especially given that in IOPD, oligodendritic accumulation of glycogen outweighs that of other glial cells (Gambetti et al. 1971). For although absolute oligodendrocyte numbers appear not to be altered in IOPD (Gambetti et al. 1971; Mancall et al. 1965), little is known about the potential impact of glycogen accumulation on oligodendrocyte function. However, given the impact of α -glucosidase has on mTOR regulation (Lim et al. 2017) and the importance of mTOR has on oligodendrocyte differentiation (Bercury et al. 2014), the potential for oligodendrocyte dysfunction in IOPD seems a worthwhile avenue worthy of further investigation.

Given that glycogen accumulation is the pivotal pathological determinant in the subcellular cascades (Lim et al. 2014), it is interesting to note that the patients with the most extensive radiological neurological involvement reported thus far, have demonstrated or would be predicted to show the lowest enzymatic activity. Thus case 1, the most severely affected of the series of Chien et al. (2006), had the lowest fibroblast, while the both the patient reported here and that in the case of Rohrbach et al. (2010), have genotypes predictive of no functional protein production. It may thus be the central nervous system involvement in part underlies the seemingly worse outcome in CRIM negative patients (Kishnani et al. 2010), with increasing suggestions that the poor outcome may not always be antibody mediated (Broomfield et al. 2016). The paradigm being that even minimal increases in glycogen clearance, affected by minimally functioning α -glucosidase results in milder CNS disease. This seems to be borne out given the variability in the amount of glycogen found in the CNS in children diagnosed in early childhood (Martini et al. 2001; Martin et al. 1976).

In conclusion, this is the earliest case of apparent progressive CNS disease documented thus far in the classical onset IOPD population, where extensive investigation has failed to find an alternative causation. It adds to the growing evidence that the CNS accumulation of glycogen in classical onset IOPD cases may not be as benign as previously considered and may indicate the need for greater surveillance of the central nervous system in the IOPD population from an early age. For although thus far the clear majority of IOPD patients have no apparent manifestations of progressive white matter involvement, CNS involvement should at least be considered in IOPD who are showing increasing functional loss, whatever their age.

Synopsis

Some patients with the classical variant of infantile onset Pompe disease run the risk of an early childhood onset progressive white matter involvement.

Details of the Contributions of Individual Authors

Dr. Broomfield conceived and was the main author of the manuscript.

Miss Fletcher: Helped collect data and has critically reviewed the manuscript.

Miss Hensman: Helped collect data and has critically reviewed the manuscript.

Mr. Wright: Both performed and analysed the data of the NGS investigations. He also critically reviewed the manuscript.

Miss Prunty performed the CSF HPLS tetrasaccharide assay and critically reviewed the manuscript.

Dr. Pavaine reviewed and selected the neuroimaging and critically reviewed the manuscript.

Dr. Jones helped collect data and conception of the manuscript and has reviewed the manuscript.

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Competing Interest Statement

Dr. Broomfield and Dr. Jones have both received travel funding, teaching Honoria from and have done consultancy for Sanofi-Genzyme. The other authors have no conflict of interest of note.

Details of Funding

No funding was involved in this study and the authors confirm that the content of the article has not been influenced by the sponsors.

Details of Ethics Approval

Not applicable, given the nature of this case report.

A Patient Consent Statement

Parental consent for the use of the images has been granted.

Documentation of Approval from the Institutional Committee for Care and Use of Laboratory Animals

Not applicable given the nature of this case report.

Appendix

Genes examined by NGS targeted panel approach:

ABCD4, ACSF3, AMN, AUH, BCKDHA, BTBD, CD320, CUBN, DBT, DHFR, DHFRL1, DNAJC19, FOLR1, FLOR2, FOLR3, FTCD, GIF, HCFC1, HLCS, IVD, LMBRD1, MCCC1, MCCC2, MCEE, MMAA, MMAB, MMACHC, MTHFD1, MTHFR, MTR, MTRR, MUT, OPA3, PCCA, PCCB, PPMIK, SERAC1, SLC19A3, SCL46A1, SLC52A1, SLC52A2, SLC5A3, SCULA2, SUCLG1, TAZ, TCN1, TCN2, TMEM70.

Unclassified variants identified through screening were the BCKDHD c.-4G>C heterozygote and PCCA C.1236A>G p.(Pro421Pro) het.

Genes examined using NGS targeted exome approach:

ACOX1, ACP5, AIMP1, ATN1, ATP7B, BCAP31, CGA, CLCN2, CLCN7, COL4A1, COL4A2, CSF1R, CTC1, DARS, DARS2, DCAF17, EARS2, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, ERCC2, ERCC3, ERCC5, ERCC6, ERCC8, FA2H, FAM126A, FARS2, FHL1, FHL2, FKRP, FKTN, GAN, GBE1, GFAP, GJA1, GJC2, GPR56, GTF2H5, HSD17B4, HSPD1, HTRA1, JAM3, LAMA2, LARGE, LMNB1, MAGT1, MARS2, MLC1, MPLKIP, NDUFS1, NOTCH3, NPC1, NPC2, NUBPL, OCLN, OCRL, OSTM1, PEX1, PEX2, PEX3, PEX5, PEX6, PEX7, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX26, PLP1, PMM2, POLD1, POLR1C, POLR3A, POLR3B, POMGNT1, POMT1, POMT2.

RNASET2, SLC16A2, SLC17A5, SLC25A12, SLC7A2, SPG5A, SPG7, SPG11, SPG15, SPG18, SPG26, SPG35, PG53, TREM2, TUBB4A, TYROBP, ZFYVE26.

Unclassified variants identified using NGS targeted exome approach:

NM_025000.3 DCAF17 c.1030T>C p.(Trp344Arg) het

NM_004366.5 CLCN2 c.1930C>T p.(Arg644Cys) het

NM_003630.2 PEX3 c.161G>A p.(Arg54Gln) het

NM_001940.3 ATN1 c.1500_1508delGCAGCAGCA p.(Gln500_Gln502del) het

NM_000053.3 ATP7B c.442C>T p.(Arg148Trp) het

NM_013382.5 POMT2 c.2223A>G p.(=) het

NM_025137.3 SPG11 c.3146-4C>A het

NM_152415.2 SPG53 c.834A.G het

Gene	% Coverage 20X	Gene	% Coverage 20X	Gene	% Coverage 20X
ACOX1	99.21	FKRP	100.00	PEX13	99.76
ACP5	100.00	FKTN	89.70	PEX14	100.00
AIMP1	95.27	GAN	97.29	PEX16	91.67
ATN1	99.66	GBE1	98.70	PEX19	99.45
ATP7B	98.34	GFAP	99.86	PEX2	100.00
BCAP31	59.10	GJA1	15.48	PEX26	100.00
CGA	100.00	GJC2	99.70	PEX3	100.00
CLCN2	100.00	GPR56	100.00	PEX5	100.00
CLCN7	100.00	GTF2H5	85.32	PEX6	99.81
COL4A1	98.73	HSD17B4	90.47	PEX7	100.00
COL4A2	99.82	HSPD1	24.58	PLP1	84.96
CSF1R	99.68	HTRA1	99.51	PMM2	98.04
CTC1	99.27	JAM3	100.00	POLD1	99.72
DARS	94.11	LAMA2	97.72	POLR1C	97.60
DARS2	98.38	LARGE	100.00	POLR3A	98.36
DCAF17	96.69	LMNB1	97.64	POLR3B	95.37
EARS2	98.87	MAGT1	71.95	POMGNT1	100.00
EIF2B1	100.00	MARS2	100.00	POMT1	98.92
EIF2B2	99.46	MLC1	100.00	POMT2	99.51
EIF2B3	99.46	MPLKIP	99.55	RARS	91.00
EIF2B4	99.90	NDUFS1	98.59	RNASET2	90.60
EIF2B5	100.00	NOTCH3	99.83	SLC16A2	90.74
ERCC2	99.57	NPC1	98.25	SLC17A5	93.60
ERCC3	98.07	NPC2	100.00	SLC25A12	96.35
ERCC5	95.65	NUBPL	87.84	SLC7A2	96.77
ERCC6	97.95	OCLN	37.50	SPG11	91.76
ERCC8	89.66	OCRL	92.60	TREM2	100.00
FA2H	100.00	OSTM1	82.40	TUBB4A	88.73
FAM126A	98.06	PEX1	95.55	TYROBP	99.77
FARS2	100.00	PEX10	100.00	ZFYVE26	98.57
FHL1	83.54	PEX11B	96.28	Grand Total	95.95
FHL2	100.00	PEX12	99.19		

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