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Infantile onset progressive cerebellar atrophy and anterior horn cell Degeneration-A novel phenotype associated with mutations in the PLA2G6 gene

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ABSTRACT

Pontocerebellar hypoplasia (PCH) encompasses a group of neurodegenerative disorders. There are ten known subtypes with common characteristics of pontine and cerebellar hypoplasia or atrophy, neocortical atrophy, and microcephaly. PCH is associated with anterior horn cell degeneration in PCH1a and PCH1b due to mutations in the VRK1 and EXOSC3 genes. Late onset PCH1 has been described in single case reports. The molecular etiology remains mostly unknown. We describe two siblings from a consanguineous Moslem Arabic family with a unique combination of progressive cerebellar atrophy and a SMA-like anterior horn cell degeneration due to a homozygous mutation in the PLA2G6 gene (NM_003560.2). The *PLA2G6* gene encodes phospholipase A2 beta, which is involved in the remodeling of membrane phospholipids, signal transduction and calcium signaling, cell proliferation and apoptosis. Mutations in PLA2G6 are known to cause Neurodegeneration with brain iron accumulation 2 (NBIA2): Our patients have some similarities with NBIA2; both are characterized by rapidly progressive psychomotor regression and cerebellar atrophy. However, NBIA2 is not known to exhibit anterior horn cell degeneration.

Our patients' phenotype is more consistent with late onset PCH1; thus, indicating that the spectrum of clinical and radiological presentations of PLA2G6 mutations should be extended and that this gene should be included in the molecular evaluation of patients with late onset PCH1.

1. Introduction

Pontocerebellar hypoplasia (PCH) encompasses a group of autosomal recessive neurodegenerative disorders. There are 12 known subtypes (PCH1-12) with common characteristics of pontine and cerebellar hypoplasia and atrophy, cortical atrophy, and microcephaly. Other mutations such as in *CASK*, *RELN* and *DKC1* genes have a comparable imaging pattern, however, they are not formally termed PCH [Hayashi et al., 2017; Hong et al., 2000; Dehmel et al., 2016].

PCH1a (OMIM 607596) and PCH1b (OMIM 614678) are distinct due to the associated anterior horn cell degeneration. Clinically, PCH1 can present in utero, with decreased fetal movements and polyhydramnios [Barth, 1993]. In the newborn period, most patients suffer from hypotonia, respiratory insufficiency, impaired swallowing and contractures. Later on, patients exhibit postnatal microcephaly, and global developmental delay with intellectual disability. Nystagmus and ataxia can also occur. Life expectancy is short and does not exceed a few months in most cases [Barth, 1993; Namavar et al., 2011a,b; Eggens et al., 2014a,b].

A rare phenotype is late-onset PCH1, starting after the first year of life. These patients have longer life spans up to 11 years. MRI shows cerebellar atrophy with anterior horn cell degeneration, without pontine involvement [Kalpana et al., 2009; Rudnik-Schöneborn et al., 2003; Jain et al., 2014]. To date, mutations in the vaccinia-related kinase 1 (*VRK1*) gene-PCH1a [Renbaum et al., 2009], in the *EXOSC3* gene-PCH1b [Eggens et al., 2014a,b], in the tRNA splicing endonuclease homolog 54 (*TSEN54*) [Simonati et al., 2011], and in mitochondrial arginyl-transfer RNA synthetase (*RARS2*) [Namavar et al., 2011a,b]

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have been identified in patients with PCH1. Recently, Braunisch et al., (2018) have suggested that mutations in the SLC25A46 gene may cause a severe form of the PCH1 phenotype.

We have previously described two siblings from a consanguineous Moslem Arabic family who presented with progressive degeneration of both the cerebellum and anterior horn cells. [https://www.ncbi.nlm.nih.gov/pubmed/?PARAMS=xik_3gPwjNwJtJDURwAVzsSdvnCK426Tj4xvowwbxPyDMfyeQoVprK1GrEUQkjApWDXSSAXpzdSZ3aYX7iKATpY7g4HLMhrS5DkgMLevsSTKQ2Yckz, Lev et al., 2008]. Recently, we preformed reanalysis of whole exome sequencing data and found a homozygous *PLA2G6* mutation in these siblings. Mutations in this gene are known to cause Neurodegeneration with Brain Iron Accumulation 2 (NBIA2; OMIM 256600). Although both syndromes are characterized by rapidly progressive psychomotor regression and cerebellar atrophy, there are no previous descriptions of anterior horn cell degeneration in NBIA2.

2. Clinical reports

2.1. Patient 1

The first child, a boy, was the product of a normal pregnancy and delivery. The parents are healthy first-degree double cousins, from Moslem Arabic origin. Birth weight was 3.5 kg and head circumference was normal. He developed normally until the age of 1 year. At that age a regression in his motor and cognitive development was noticed. He did not start walking; he could no longer sit without support and became unstable. He did not develop language. Evaluation at the local child development center was normal. He had normal repeated ophthalmoscopic examinations with normal fundi. Nerve conduction and electromyography EMG were initially normal. Brain MRI showed reduced size of the vermis and cerebellar hemispheres, normal brainstem and an enlarged fourth ventricle and cisterna magna (Fig. 1). The ventricular system, myelination and gray matter structures; basal ganglia and thalamus were normal. No radiographic changes typical of iron accumulation were visible. Over the following years he did not achieve any developmental progress and his condition deteriorated slowly. The patient was first seen at our neurogenetic clinic at the age of 5 years. He laid almost motionless in a supine frog position. He could sit with support and eat with a spoon. He smiled but made poor eye contact. Horizontal nystagmus was prominent. He was mildly dysmorphic with hypertelorism, long eyelashes, hypertrichosis and prominent ears. Head circumference was 52 cm (50th percentile). Moderate kyphosis was noted. He recognized his family members and understood simple commands. There was no speech and he

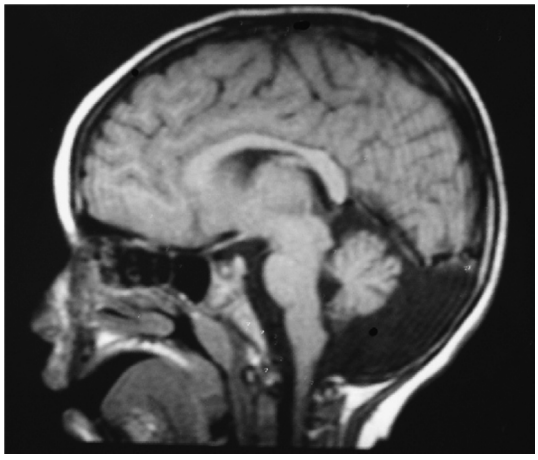

Fig. 1. Brain MRI of patient 1, at the age of 2 years: T1 midsagittal image demonstrates enlarged cisterna magna with atrophic vermis. The pons is preserved [Lev et al., 2008].

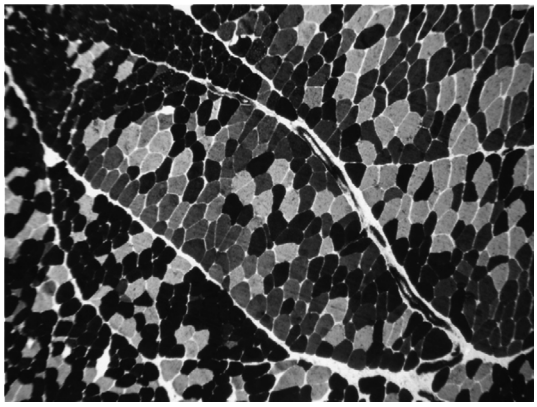

Fig. 2. Transverse section of muscle, ATPase at pH 9.4 stain, showing type-grouping [Lev et al., 2008].

communicated by making guttural sounds. Neurological examination demonstrated axial hypotonia but increased appendicular tone with brisk tendon reflexes, clonus and extensor plantar responses. He had neither tongue fasciculations nor tremor. The leg muscles were atrophic. There was no withdrawal to painful stimuli. He had arm dysmetria with athetoid movements. An examination at the age of 7 years old revealed progressive deterioration; he could no longer sit with support; he could not communicate. At the age of 12 years, he still recognized his family, ate with assistance, and breathed on his own. He died of respiratory insufficiency at that age. Nerve conduction at the age of five years was normal. A muscle biopsy done at the same time, taken from the quadriceps muscle demonstrated chronic neurogenic changes: predominance of type II fibers and group atrophy and mitochondrial morphological changes (Fig. 2). Mitochondrial staining and respiratory chain enzyme activities were normal. A nerve biopsy was normal, no spheroid bodies were seen.

2.2. Patient 2

The younger sister, now an 18-year-old girl, was born after 39 weeks of pregnancy following a normal delivery; birth weight was 3.3 kg, head circumference was normal. The postnatal period was normal as were early developmental milestones: she stood at 13 months and walked independently; she said her first words at 10 months and talked in two-word sentences by the age of 2 years. She was referred to the child development center at the age of 26 months old due to slowing of her development and cerebellar signs. Her neurological exam at that time showed prominent intention tremor, ataxic gait and increased reflexes with extensor plantar responses. Her developmental quotient was 66. A brain CT showed cerebellar atrophy and large cisterna magna. Examination at the neurogenetic clinic at the age of 3.5 years demonstrated similar dysmorphic features resembling her brother with hypertelorism, long eyelashes and hypertrichosis. Physical development was at the 50th percentile. She understood simple commands and communicated by single words or two-word utterances. She could no longer walk, and she crawled by pulling herself with her hands and passively moving her feet. She sat without support with a kyphotic back. There were axial hypotonia with increased appendicular tone, brisk tendon reflexes, and ankle clonus. Examination at the age of 4.5 years revealed developmental deterioration. She could no longer crawl; she could still sit with support. She used only a few words and communicated with simple gestures. An MRI which was done at the age of 6 years showed a markedly reduced size of the vermis and cerebellum with enlarged fourth ventricle and cisterna magna (Fig. 3, Fig. 4). The brain stem was preserved. In comparison to the CT done three years earlier, cerebellar atrophy had progressed, now resembling her brother's MRI. At the age of 7 years she stopped talking and soon after she stopped communicating via gestures. At 14 years, a tracheostomy was

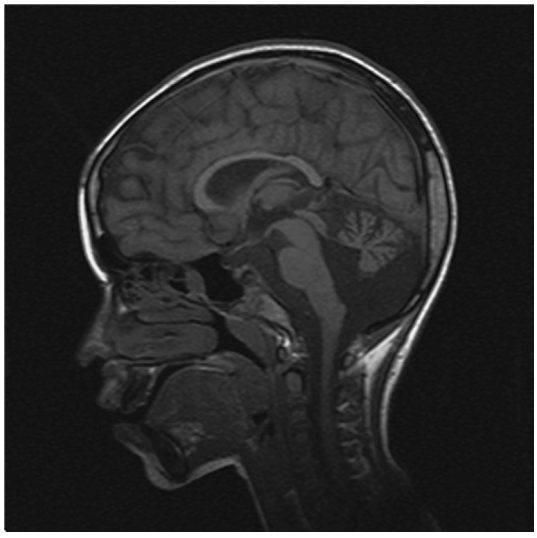

Fig. 3. Brain MRI of patient 2 at the age of 6 years: T1 midsagittal section demonstrates a small and atrophied vermis with deep folia and enlargement of the 4th ventricle. Thalamus, brain stem and cortex are normal [Lev et al., 2008].

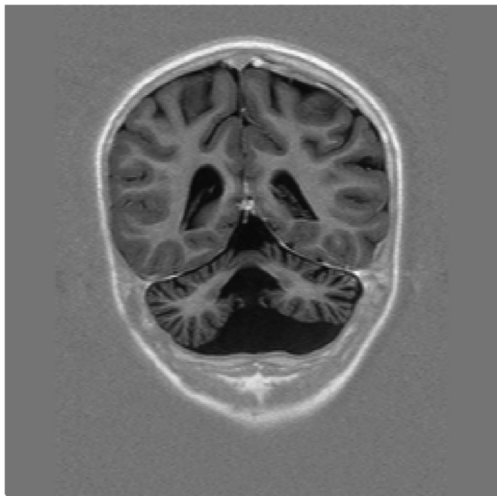

Fig. 4. Brain MRI of patient 2 at the age of 6 years: T1 coronal TIR image demonstrates atrophy of the cerebellar hemispheres and vermis, enlargement of the 4th ventricle and cisterna magna and deep folia [Lev et al., 2008].

inserted for mechanical ventilation, and a gastrostomy for feeding. To date, at the age of 18 years she does not make eye contact, but reacts to her family's voices with a smile, which is the only communication she makes. She has no developmental achievements. She is mechanically ventilated and fed through the gastrostomy.

3. Methods

Written informed consent was obtained from all family members, in accord with the standards of the institutional review board. Genomic DNA was extracted from peripheral blood by the QIAamp DNA Mini kit (QIAGEN), according to the manufactures' instructions.

3.1. Exome sequencing

Whole exome sequencing was performed on the patients' DNA. The sample was enriched with Sureselect Human All Exon V5 kit 50 Mb (Agilent, Santa Clara, CA, USA). Sequencing was carried out on HiSeq4000 (Illumina, San diego, CA, USA) as 100-bp paired–end runs. Reads were aligned with the human reference genome (assembly GRCh37/hg19). Pipeline was performed using the Genoox platform based on BWA (version 0.7.16) for read alignment and GATK HaplotypeCaller (version 3.7) and FreeBayes (version 1.1.0) for variant calling.

Dataset files including the annotated information were analyzed with the following filtering steps: variants which were called less than 9 times and synonymous variants were removed. Variants were filtered based on allele frequency less than 0.01 according to online databases; dbSNP, 1000G, ExAC and gnomAD. Likely pathogenicity was assessed if the variant was truncating (splicing or non-sense), missense or an in-frame indel. Missense and in-frame indels were considered if they were predicted to be pathogenic by online prediction tools, PolyPhen-2, SIFT and Mutation Taster. Conformation and familial segregation were performed using direct Sanger sequencing (3500 Genetic Analyzer Applied Biosystems).

4. Results

The WES analysis revealed a homozygous variant in *PLA2G6* (NM_003560.2):

c.2251G > A; p.Glu751Lys in both siblings. The variant was validated in the two siblings by Sanger sequencing, and familial segregation showed that both parents are heterozygous carriers, the healthy brother is also a heterozygous carrier and the healthy sister does not carry the mutation at all (Table 1). This variant, p.Glu751Lys, has been previously described in a patient with a neurodegenerative disorder with brain iron accumulation by Morgan et al., [2006] and published in a public database HGMD – PUBLIC, accession number CM063028. The variant is extremely rare and has been reported in gnomAD only in one heterozygous carrier, it is fully conserved among different species and is predicted to be deleterious by in silico prediction tools.

5. Discussion

Barth, was the first to describe in 1993 an association between cerebellar atrophy and anterior horn involvement, naming this disorder PCH1. Later on, patients with later onset PCH1 and a more benign course have been described. Parisi and Dobyns [2003] suggested that pontocerebellar hypoplasia, should be more accurately termed pontocerebellar atrophy, beginning postnatally, based on serial neuroimaging studies and clinical heterogeneity. Wilmshurst et al., [2000] reported four children with cerebellar ataxia and anterior horn cell disease who were diagnosed by 3 years of age after normal early development. Genetic studies suggested that the condition was not allelic with SMA. Rudnik-Schöneborn et al., [2013] described the phenotypic variability among families with pontocerebellar hypoplasia's type 1 including a longer life span beyond early childhood, and radiographically a relative sparing of the brainstem, similar to our patients. Additional case reports of patients with later onset of symptoms and evidence of anterior horn cell degeneration in addition to pontocerebellar atrophy were described by Sanefuji et al., [2010], Yi Qian et al., [2014] and Jain et al., [2014]. . These cases suggest that PCH1 can present with normal early development, a milder progressive course and longer lifespan. The genetic basis of most of these patients has not been elucidated. We suggest naming this entity late onset PCH.

Homozygous mutation in the PLA2G6 gene was found in our patients. This gene encodes the calcium dependent phospholipidase A2 beta, which hydrolyses glycerophospholipids to release free fatty acids and lysophospholipids. The PLA2G6 protein is localized in the mitochondria and has suggested roles in the remodeling of membrane phospholipids, signal transduction, calcium signaling, cell proliferation and apoptosis. Mutations in *PLA2G6* lead to lipid peroxidation, mitochondrial dysfunction and subsequent mitochondrial abnormalities, which are highly vulnerable for neuro axonal survival [Kinghorn et al., 2015]. PLA2G6 mutations are known to cause NBIA2 In NBIA2, the

Table 1
The clinical findings of our patients in comparison with those of the patients described in the literature with late onset PCH1 and *PLA2G6*-NBIA2 (based on a table in an article by Romani et al. [2015]

Patients	1	2	PCH1 late onset (19 patients)	PLA2G6 NBIA2 (17 patients)
Sex	M	F	M/F	M/F
Origin	Israeli Moslem	Israeli Moslem	German, Pakistani, Turkish, Indian, Japanese, Chinese	North African
Consanguinity	yes	yes	yes/no	yes/no
Protein change	Glu751Lys, c.2251G > A	p.Glu751Lys, c.2251G > A	p.Gly31Ala p.Val80Phe p.Asp132Ala p.Ser93Pro p.Ala307Ser p.Gln246Ter p.Gln343Ter p.Val236Met	p.Val691del Val691del + Leu481Gln Glu786fs*29 His124_Ala126dup + Arg635Ter Glu547Gly Arg645Pro Arg741Trp Phe568Val
AAO (years, months)	9 months	26 months	3 months- 30 years	6 months-3 years
First symptoms	PM regression	PM arrest, cerebellar signs	muscle weakness or developmental delay	PM regression (1st sign)
Last follow up (years, months)	12	18		
Hypotonia	moderate (axial)	mild (axial)	moderate	moderate (early)
Pyramidal signs	severe (appendicular)	severe (appendicular)	moderate (contractures)	moderate (late)
Cognitive decline	severe	moderate	moderate	moderate
Nystagmus/ strabismus	ny(horizontal)	Not available	ny	ny, strabismus
Optic atrophy	no (age 9 months)	Not available	no	yes
Cerebellar signs	no (dysmetria)	yes	yes	yes
Achilles tendon areflexia	no	no	not described	yes
Other signs	amyotrophy, dysmorphism, no language, normocephaly	amyotrophy, dysmorphism, normocephaly	progressive microcephaly, Anterior horn cell degeneration	no micro/macrocephaly described

† AAO- age of onset. ‡ F-female, M-male. § ny-nystagmus. ¶ PM-psychomotor.

children typically develop normally until the age of 6–18 months old. They then experience a rapidly progressive psychomotor regression, truncal hypotonia and tetra paresis. Ophthalmological involvement including strabismus, nystagmus, and optic atrophy is common. In Table 1 (Table 1) we describe the clinical findings of our patients in comparison with those of the patients described in the literature with late onset PCH1 and *PLA2G6*-NBIA2 (based on a table in an article by Romani et al., [2015]). The similarities of the phenotype of our patients with NBIA2 are: the patients are normocephalic; the age of onset is usually after the age of one year; cerebellar signs are the first manifestation; they later develop neurogenic weakness and psychomotor regression.

However, unlike our patients with late onset PCH1, patients with NBIA2 do not exhibit anterior horn cell involvement, nerve conduction is abnormal and shows a distal axonal sensorimotor neuropathy [Gregory et al., 2008, updated 2017]. Furthermore, a peripheral nerve biopsy in patient 1 was normal (as seen in other patients with PCH1, described by Renbaum et al., [2009]) as opposed to nerve biopsies in patients with *PLA2G6* mutations, that exhibit spheroid bodies, membrano-tubular profiles, mitochondrial aggregates and increased axonal diameter and thinned membrane on electron microscopy [Gregory et al., 2008, updated 2017]. Radiographically, our patients' MRI scans are compatible with late onset PCH1 and not NBIA2. Both disorders demonstrate cerebellar atrophy but the typical radiographic features of NBIA2 represented by iron accumulation, cerebellar cortex hyperintensity and basal ganglia changes, are lacking in our patients [Illingworth et al., 2014; Al-Maawali et al., 2016].

Although our patients demonstrate some similarities with NBIA2, their phenotype is more consistent with late onset PCH1; thus, indicating that the spectrum of clinical and radiological presentations of *PLA2G6* mutations should be extended and that this gene should be included in the molecular evaluation of patients with late onset PCH1.

Declaration of competing interest

The authors declare they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2019.103801.

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