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University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Video is part of this manuscript

The first report of putaminal cysts in the familial series of dystonia associated with Salla Disease-the phenotype expanded.

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Salla disease (SD) is an autosomal recessive, lysosomal storage disorder first described in 1979 and named after a small municipality in Finland.[1] SD is caused by mutations in the *SLC17A5* gene encoding sialin a protein responsible for sialic acid transport across lysosomal membranes and CNS myelination.[2] Individuals typically present after six months of age with hypotonia, ataxia, developmental delay, and hypomyelination, followed by slowly progressive neurological deterioration and nearly normal lifespan.[3] Despite over 200 reported cases, many aspects remain poorly understood due to its rarity and limited geographic diversity.

Case report

We report the first Irish family with genetic confirmation of Salla disease. The family consists of six siblings born to non-consanguineous parents, five symptomatic.

The proband, a 48-year-old man (III-4, Video 1), had poor head control and impaired balance in infancy. He did not crawl until age two or walk until six. Myoclonus, dystonia and ataxia were prominent from five years. Speech was limited (short phrases), and he required special schooling. He remained stable until his mid-30s, when cognitive and motor decline emerged.

By age 48 he had spasticity of the lower limbs, gait ataxia, pyramidal weakness, tremor (head upper limbs), bilateral foot dystonia, dysarthria, dysphagia, and impaired executive and social function.

Extensive investigations, including metabolic screening (in particular, lysosomal storage disorders, aminoacidopathies, and mitochondrial diseases), cerebrospinal fluid analysis, muscle and skin biopsy (for mitochondrial disease and Lafora disease) were unrevealing.

MR imaging showed hypomyelination (proband's imaging was performed >20 years ago and is not available). Whole exome sequencing revealed

homozygous *SLC17A5* p.K136E (c.406A>G) pathogenic variant confirming Salla disease.

Four siblings developed similar phenotype (Figure 1, Video 1 and 2), one remained asymptomatic (III-2). All affected siblings were born at a normal gestation without complications and had infantile hypotonia, delayed milestones, psychomotor impairment requiring special schooling. Motor regression requiring walking aids in the third to fifth decades was noted in four of the five patients (III-1, III-3, III-4, III-5, and III-6). Speech development was impaired with spastic dysarthria and regression in subsequent years. Facial coarsening and hypertelorism were present. Two developed epilepsy in their 20s. Four had stimulus sensitive myoclonus with age of onset in early childhood, most pronounced in their 20s and 30s.

Bedside examination confirmed spasticity, executive dysfunction and impaired social cognition. Two of the five patients (III-1 aged 43; III-5 aged 47) died from aspiration pneumonia secondary to impaired bulbar function in the fifth decade of life.

Genetic testing confirmed homozygous *SLC17A5* p.K136E (c.406A>G) pathogenic variant in all five affected, with parents as asymptomatic carriers (normal examination), MRI brain showed hypomyelination in all, and putaminal cysts in two siblings (Fig 2, III-3, III-5).

Discussion

We present the first Irish report of Salla disease and describe the novel radiological feature of putaminal cysts. The predominant phenotype in our family included ataxia, spasticity, and dystonia.

While ataxia and spasticity are well-documented in Salla disease, dystonia is rarely reported, with only ten cases described worldwide including in one sibling pair. [4,5]

With five affected siblings, our series represents one of the largest familial clusters of dystonia associated with Salla disease.

We additionally report myoclonus in four siblings, an observation not previously documented to our knowledge. This was noted consistently during 25 years of follow-up (BS), particularly in early adulthood (ages 20-30s), and partially remitted in later years. The longitudinal nature of this observation strengthens its validity despite retrospective assessment and lack of video documentation.

The genetic mutation identified in our patients (p.K136E) has only been reported in four other homozygous cases.[3,4]

Clinical features in those cases overlapped with our patients, including early-onset ataxia, hypotonia, and developmental delay in a 3-year-old girl, and a 5-year old boy who also exhibited nystagmus and intention tremor. In contrast, two other reported patients —a 19-year-old man and a 12-year-old girl—had intellectual disability but, showed no movement disorders or seizures.[3,4]

By contrast, the majority of Finnish patients carry the founder R39C mutation, reflecting a strong geographic concentration (carrier frequency of 1:100) in northeastern Finland.[6,7]

Only 35 out of the 204 documented cases of intermediate severe Salla disease worldwide have detailed MRI findings. Among these, hypomyelination and corpus callosum hypoplasia remain the hallmark of Salla disease [8,9] Our identification of putaminal cysts expands the imaging phenotype. [9,10] While symmetrical putaminal necrosis as seen in Leigh syndrome cannot be entirely excluded, the well-circumscribed (unlike in Leigh syndrome), CSF-like signal of the lesions without diffusion restriction, gliosis, or edema, and stability across serial MRIs four years apart in III-5 strongly favor cystic nature rather than necrosis.

We hypothesize that sialic acid accumulation in Salla disease leads to impaired lysosomal homeostasis, disrupted autophagy, progressive neuronal and glial dysfunction, and hypomyelination further weakening deep gray and white matter, predisposing to cystic degeneration in vulnerable regions such as the basal ganglia. In this slowly progressive leukodystrophy, the lesions therefore reflect structural vulnerability rather than acute necrosis. Although putaminal cysts could contribute to dystonia, none have been

reported among the 10 published cases of dystonia in Salla disease.

Although we were unable to capture myoclonus, prior to this study, only ten patients with Salla disease have been published with clinical images (no videos).

Although rare, Salla disease should be considered in patients with progressive developmental delay and hypomyelination on MRI. By describing familial dystonia in siblings, and reporting putaminal cysts on MRI for the first time, this report broadens the clinical and radiological phenotype of Salla disease.

These findings emphasise the need for heightened clinical suspicion and comprehensive evaluation in patients presenting with developmental delay and movement disorders, regardless of geographic background.

Author roles:

1. Research project: A. Conception, B. Organization, C. Execution;

2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

EM 1B, 1C, 3A,3B

AOC 1C, 3B

NF 3C

BS 1A, 1C, 3B

DAO 1A, 1B, 1C, 3B

Disclosures:

- ***Funding Sources and Conflict of Interest:***

No specific funding was received for this work.

The authors declare that there are no conflicts of interest relevant to this work.

- ***Financial Disclosures for the previous 12 months:***

Ethical compliance statement

We confirm that we have read the Journal's position on issues involved in ethical

publication and affirm that this work is consistent with those guidelines.

Written, informed consent was obtained from all participants of the study

EM declares no financial support

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NF declares no financial support

BS declares no financial support

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Ethical Compliance Statement

The authors confirm that the approval of an institutional review board was not required for this work.

Informed, written consent was obtained from all participants and the next of kin.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Figure 1 legend

Family pedigree

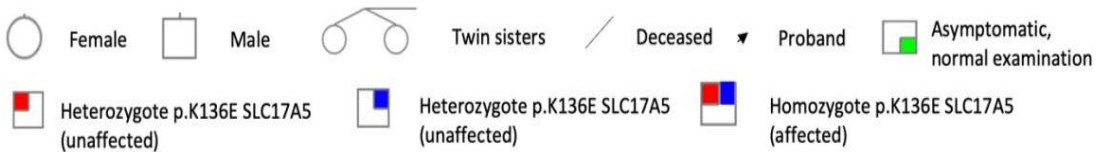

Figure 2 legend

MRI of his four siblings, III-5 (A-D), III-3 (E-H), III-1 (I-L) and III-6 (M-P). All four siblings show signs of hypomyelination with homogeneous moderately elevated signal in the cerebral white matter on the T2-weighted images (first two columns). There is bilateral posterior putaminal hypointense signal on the susceptibility weighted imaging in all four siblings (C, G, K, O) (dotted arrow) with putaminal cyst formation in III.5 (B) and sibling III-3 (F) (arrows). There is significant global atrophy with prominent involvement of the corpus callosum and vermis in all siblings (fourth column).

Video 1 legend

Video 1 demonstrates two of three alive and affected siblings. Limited examination due to severe cognitive disability. Video III-3 shows the absence of tremor during drawing spirals, slight dystonic posturing of the hands, normal tone, past pointing on right finger-nose, ataxic gait, III-3 (proband) dystonic tremor of the head and hands, hypersalivation, normal tone, ataxic gait.

Video 2 legend

Video 2 demonstrates the third affected sibling. Video III-6 shows writing attempt, normal tone, dystonic tremor of the hands, slight kinetic tremor of the right hand, left hand past pointing possibly related to comprehension difficulties, spastic gait.