Phenotypic Heterogeneity of ISCA2 Variants

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Abstract

ISCA2 variants have been recently reported to be responsible for a multisystem mitochondrial disease, predominantly affecting the central nervous system. The largest series of patients has been recently reported but it lacks prospective investigations for multiorgan involvement and specification of spinal cord involvement.

Keywords - *ISCA2, mitochondrial, mtDNA, cerebrum, neurodegeneration, multisystem*

I. INTRODUCTION

In a recent article, Alfadhel et al. presented the results of a retrospective study about 10 patients from 9 unrelated Saudi families carrying an *ISCA2* variant which manifested phenotypically with the triad of neurodevelopmental regression, nystagmus with optic atrophy, and diffuse white matter lesions in the brain, cerebellum, and spinal cord [1]. There was consanguinity between the parents of all included patients [1]. The study raises the following comments and concerns about the specificity of the information provided.

II. DISCUSSION

Involvement of the spinal cord is a frequent feature of *ISCA2* variants, why the condition is frequently mixed up with leukoencephalopathy with brain and spinal cord involvement, and lactic acidosis (LBSL) [2]. However, involvement of the spinal cord in mitochondrial disorders (MIDs) may not only occur in patients carrying *ISCA2* variants or suffering from LBSL but also in specific MIDs such as Leigh-syndrome, MERRF, KSS, IOSCA, MIRAS, PCH6, MELAS, CPEO, or LHON [3]. Additionally, the spinal cord may be affected in patients carrying variants in the *SURF1, tRNA(Glu),* or *POLG1 g*enes respectively [3].

The authors found spinal cord involvement in 7/9 of their patients, reported as "abnormal spinal cord signalling" without specification neither of the MRI image modalities applied nor the spinal cord structures affected (table 1) [1]. To properly interpret the phenotype, it is essential to know which structure (pyramidal tract, spinocerebellar tracts, posterior columns, rubrospinal tracts, Clarke's column, grey matter, white matter etc.) was indeed affected. Were there hypointensities or hyperintensities on T1, T2, FLAIR, TIRM, DWI, ADC, PWI, or T1 with contrast medium?

So far, 19 patients with *ISCA2* variants have been published [1,4,5,6]. Ten patients were reported by Alfadhel et al. in the current study (c.229G>A, homozygous) [1], 6 by Al-Hassnan et al (c.334A>G, c.229G>A, compound heterozygous) [4], two patients by Alaimo et al. (c.229G>A, homozygous), and one patient by Toldo et al. (c.295delT, c.334A>G, compound heterozygous. The mutation described by Al-Hassnan et al. resulted in mtDNA depletion and complex-I-deficiency [4]. MtDNA depletion was also found in fibroblast from the two patients reported by Alaimo et al. [6]. Were the ten patients reported by Alfadhel et al. investigated for mtDNA depletion and by which amount was the mtDNA depleted compared to normal? To which degree was mtDNA depletion made responsible for the entire phenotype or part of the phenotype?

Table 1. Phenotype of ISCA2 variants reported in the literature

Organ/system/abnormalities	Reference
Central nervous system	
Infantile-onset leukodystrophy	[1,6]
CSF glycine ↑, CSF pyruvate ↑ CSF serine ↑	[1,6]
CSF glutamate ↑, 5-MET ↓	[6]
Optic atrophy	[1]
Nystagmus	[1]
Loss of fixation	[1]
Delayed developmental milestones	[1,6]
Cerebellar white matter lesions	[1]
Spinal cord involvement	[1]
Seizures	[1]
Spasticity	[1]
Hypotonia	[1]
Dysphagia	[1]
DWI abnormalities in cerebral white/grey matter	[5]
Gastrointestinal	
GERD	[1]
Feeding difficulties	[6]
Aspiration	[6]
Constipation	[6]
Endocrine system	
Recurrent miscarriages	[1]
Growth retardation	[6]
Muscle	
Myopathy (fibre size variability ↑, fiber atrophy)	[4]
Complex-I-deficiency in muscle	[1]
Dysmorphism	
Low set ears	[6]
Broad nasal bridge	[6]
Other	
Vesicoureteric reflux	[1]
Joint laxity	[6]
Short fourth metacarpals	[6]

Cutaneous toe syndactyly	[6]
Serum lactate ↑	[1,6]
Serum glycine ↑	[1,6]
Serum chitotriosidase ↑	[6]
Serum palmytoyl-thioesterase ↓	[6]
Serum B-glucosidase ↓	[6]
Serum arylsulfatase A ↓	[6]
Visual impairment	[6]

GERD: gastro-esophageal reflux disease

In 7 patients so far reported, *ISCA2* mutations were compound heterozygous and in 12 patients homozygous [1,4,5,6]. For patients homozygous for the mutation it can be assumed that both parents carried the mutation on one allele. Was this the case in the 18 parents of the 10 patients reported by Alfadhel et al.? Did any of the heterozygous parents manifest clinically?

All patients presented with optic atrophy [1]. Was optic atrophy diagnosed upon ophthalmologic investigations, upon MRI of the orbita, or upon both? Optic atrophy was reported to have been associated with "visual failure" [1]. Does "visual failure" reflect blindness or reduced visual acuity? How was vision tested in the babies? Were latencies of visually-evoked potentials prolonged or was the VEP-amplitude reduced?

III. CONCLUSIONS

In summary, this study could be more meaningful if organs other than the brain would have been investigated prospectively for mild clinical or subclinical involvement, if all parents would have been genetically investigated, if spinal cord involvement would have been specified, if diagnostic procedures for optic atrophy would have been reported, and if all patients so far reported would have been included in the discussion.

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