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Multiple Mitochondrial Dysfunctions Syndrome 4 Due to *ISCA2* Gene Defects: A Review

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Abstract

Multiple mitochondrial dysfunctions syndrome 4, caused by *ISCA2* gene defects (OMIM #616370), was first described by Al-Hassnan et al in 2015. To date, 20 cases have been reported: 13 females and 7 males from 18 different families. All cases are from Saudi Arabia except those from one Italian family. Typically, the patients have normal antenatal and birth history and attain normal development initially. Rapid deterioration occurs between 2 and 7 months of age, with the triad of neurodevelopmental regression, optic atrophy with nystagmus, and diffuse white matter disease. Magnetic resonance imaging findings include 75% of patients have cerebellar white matter abnormalities, and the spinal cord was affected in 55%. Magnetic resonance spectroscopy showed elevated glycine peaks in 2 (10%) cases and elevated lactate peaks in 5 (25%) cases. Biochemical abnormalities include high cerebrospinal fluid glycine and lactate and high plasma glycine and lactate, but these findings were not consistent. Diagnosis is based on the detection of biallelic mutations in the *ISCA2* gene. To date, no curative treatment has been discovered, and disease management is exclusively supportive. In this report, the authors review the published cases of *ISCA2* gene defects and retrospectively characterize disease phenotypes, the affected biochemical pathways, neuroradiological abnormalities, diagnosis, genetics, and treatment.

Keywords

ISCA2, multiple mitochondrial dysfunctions syndrome, mitochondrial disorders, iron–sulfur clusters, white matter disease

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Mitochondrial diseases can be caused by mutations of nuclear or mitochondrial DNA.[1,2] The multiple mitochondrial dysfunctions syndrome (MMDS) is a group of mitochondrial disorders caused by nuclear gene defects. They are inherited in an autosomal recessive manner. Six MMDSs have been described so far. These include MMDS1, which is caused by the *NFU1* gene defect (OMIM #605711); MMDS2, which is caused by the *BOLA3* gene defect (OMIM #614299); MMDS3 due to the *IBA57* gene defect (OMIM #615330); MMDS4 due to the *ISCA2* gene defect (OMIM #616370); MMDS5 due to the *ISCA1* gene defect (OMIM #617613); and MMDS6 due to the *PMPCB* gene defect (OMIM #617954).[3-9]

Multiple mitochondrial dysfunctions syndrome 4 (MMDS4; *ISCA2* gene defect; OMIM #616370) is one of the MMDS. The MMDS4 shares most of the clinical and biochemical features and has a defect in the same metabolic pathway as the other types. This review will discuss the history of the knowledge of the *ISCA2* gene defect, its pathophysiology, clinical phenotypes, diagnostic approach, and future implications.

History

Multiple mitochondrial dysfunctions syndrome 4 was first described by Al-Hassnan et al in 2015 reporting 6 patients from 5 unrelated consanguineous families. In 2015, Alazami et al also described a single patient from a large cohort of consanguineous families in which 33 recessive novel genes were identified, not previously associated with

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any diseases. Subsequently, in 2017, Alfadhel et al reported 10 new patients with similar phenotypes. Other researchers have described 3 more patients with overlapping phenotypes.[7,8,10-12]

Pathophysiology

The mitochondrial iron–sulfur clusters pathway is essential for the biosynthesis of *iron–sulfur*-containing proteins in the mitochondria, cytosol, endoplasmic reticulum, and nucleus.[13-15] In eukaryotes, iron–sulfur clusters are found in 2 forms: rhombic [2Fe-2S], and cubane [4Fe-4S].[16] The proteins ISCA1, ISCA2, and IBA57 carry out the maturation of all cellular [4Fe-4S] clusters and carry them to their apoproteins either directly or through other specific proteins, such as NFU1, NUBPL, and BOLA3, which contribute to the maturation of specific [4Fe-4S]-containing proteins.[17] One of the biochemical abnormalities of ISCA2 gene defects that has been observed is hyperglycinemia. This occurs due to defects in the iron–sulfur clusters pathway that leads to the inhibition of lipoic acid synthase that is vital for the glycine cleavage system, an impairment of which results in hyperglycinemia. Lipoic acid is a vital cofactor for 5 redox reactions in humans: 2 enzymes are essential for energy production (α-ketoglutarate dehydrogenase, pyruvate dehydrogenase, and 3 contribute to amino acid pathways [branched-chain ketoacid dehydrogenase, BCKDH], 2-oxoadipate dehydrogenase, and the glycine cleavage system).[18]

Functionally, the ISCA2, ISCA1, and the IBA57 proteins are involved in the assembly of a mitochondrial iron–sulfur cluster [4Fe-4S], which is important for electron transfer and mitochondrial function.[17] There is a strong interaction between the ISCA1 and the ISCA2 proteins, yet the functional significance of this interaction is still unknown. The ISCA1 is required for the maturation of mitochondrial Fe4S4 proteins in mature skeletal muscle, whereas ISCA2 and IBA57 are not required in the 2 postmitotic cell types, under standard physiological conditions.[19]

Using in vivo studies, specific interactions of the ISCA1 and ISCA2 with different proteins such as IBA57, GLRX5, and NFU1 of the late mitochondrial machinery have been described. However, there is a strong interaction observed between the ISCA2 and the IBA57, while neither IBA57 nor ISCA2 knockdown causes Fe-S metabolism phenotypes.[19] Interestingly, mutations in the IBA57 and ISCA2 in humans cause disorders in early age, suggesting association with development processes.[6] Using the {2Fe-2S} cluster, IBA57 forms a heterodimeric complex with the ISCA2, which is essential for the formation of the complex.[20]

Furthermore, ISCA1 strongly interacts with the NFU1, suggesting its association with the ISCA1 in Fe4S4 assembly. Previously, NFU1 has been reported to cause MMDS with respiratory complex, suggesting mitochondrial Fe4S4 biogenesis.[5,21]

Clinical Phenotypes

Table 1 summarizes the clinical features of *ISCA2* gene defects. To date, 20 cases have been reported from 18 different families: 13 females and 7 males. All cases, except for 1 Italian family, are from Saudi Arabia. Typically, the patients have had normal antenatal and birth histories and attain normal development initially, before showing rapid deterioration between the ages of 2 and 7 months with a triad of neurodevelopmental regression, optic atrophy with nystagmus, and diffuse white matter disease. Spasticity and axial hypotonia present in 95% (n = 19) and 65% (n = 13) of probands, respectively. Typically, by the age of 1 to 2, the patients are in a vegetative state; this can continue for years. During that period, the probands are prone to recurrent chest infections that can require ventilator support. Most cases reported died during early childhood.[7,8,10-12,22]

Seizures have been reported in 15% (n = 3) of cases reported in the literature. Two patients have generalized tonic–clonic seizures while the third one had focal seizures.[8] Other manifestations reported include relative macrocephaly, joint laxity, short fourth metacarpals, and cutaneous toe syndactyly.[11]

Neuroradiological Findings

Magnetic resonance imaging scans of the brain were carried out in all the patients and showed diffuse bilateral white matter involvement. Cerebellar white matter abnormalities were presented in 75% (n = 15) of the patients, and the spinal cord was affected in 55% (n = 11). In general, no structural abnormalities were observed, with signal abnormalities being predominant. Magnetic resonance spectroscopy, which to our knowledge was done in 13 (65%) patients, showed elevated glycine peaks in 2 (10%) cases and elevated lactate peaks in 5 (25%) cases.

Biochemical Abnormalities

Elevated lactate is a vital marker in the diagnosis of individuals with a suspected mitochondrial disease. To our knowledge, cerebrospinal fluid glycine was tested in only 3 of the 20 patients and was observed to be increased in all 3 (100%) patients. Plasma glycine was tested in 13 of 20 patients and was observed to be increased in 3 (23%) patients.[8,10,11] Therefore, both (glycine elevation on cerebrospinal fluid and plasma glycine) could be tested in other patients as potential biomarkers.

Other biochemical investigations, such as tests for ammonia, acylcarnitine profile and screening urine for organic acids, were unremarkable. Respiratory chain enzymology was checked in 2 (10%) patients and both showed complex II and IV deficiency. Muscle biopsies were done in a few patients, and revealed mild histopathological abnormalities, including myofiber size variation and atrophic changes. The mitochondria were observed to be shortened, and the outlines were stretched

Table 1. Clinical Characteristics of Patients With an *ISCA2* Gene Defect.

	Al-Hassnan et al, 2015	Alazami et al, 2015	Alfadhel et al, 2017	Alaimo et al, 2018	Toldo et al, 2018	Total, %
No. of patients	6	1	10	2	1	20
No. of families	5	1	9	2	1	18
Female:male ratio	4:2	1:0	6:4	1:1	1:0	13:7
No. of siblings or relatives who died of a similar condition	5	5	5	8	0	23
Origin	Saudi	Saudi	Saudi	Saudi	Italy	Saudi; 19/20 (95%)
Age at onset (months)	3-7	NA	3-7	3 and 6	2	
Common clinical features						
Neurodevelopmental regression	6/6	1/1	10/10	2/2	1/1	20/20 (100%)
Global developmental delay	6/6	1/1	10/10	2/2	1/1	20/20 (100%)
Spasticity	6/6	NA	10/10	2/2	1/1	19/20 (95%)
Optic atrophy	6/6	NA	10/10	2/2	0/1	18/20 (90%)
Nystagmus	NA	NA	10/10	2/2	1/1	13/20 (65%)
Axial hypotonia	NA	NA	10/10	2/2	1/1	13/20 (65%)
Seizure	NA	NA	3/10	0/2	0/1	3/20 (15%)
Mortality rate	4/6	1/1	5/10	1/2	1/1	12/20 (60%)
MRI and MRS findings						
Diffuse bilateral cerebral WM	6/6	1/1	10/10	2/2	1/1	20/20 (100%)
Cerebellar WM	3/6	NA	9/10	2/2	1/1	15/20 (75%)
Spinal cord	1/6	NA	7/10	2/2	1/1	11/20 (55%)
Molecular genetics findings						
Type of mutation	Homozygous missense mutation			Compound heterozygous mutation		
ISCA2 gene defect	c.229G>A (p.Gly77Ser)			[(c.295delT (p.Phe99Leufs*18); c.334A>G (p.Ser112Gly)		

Abbreviations: MRI, magnetic resonance imaging; MRS, MR spectroscopy; NA, not available; WM, white matter.

out and angulated. There was severe mitochondrial depletion in the fibroblasts of the patients.[7] However, myopathic features such as fiber hypertrophy or degeneration were absent, and there were no ragged red fibers.[7,11]

Genetics

The *ISCA2* gene is located at chromosome 14q24.3. The *ISCA2* gene has 4 exons, 154 amino acids, and a molecular mass of 16 476 Da. It encodes an A-type iron–sulfur cluster protein in mitochondria. This protein is essential in the maturation of mitochondrial iron–sulfur proteins. Two transcript variants encoding different isoforms have been found for this gene. Two mutations have been detected in 18 different families: one is a homozygous missense mutation (c.229G>A; p.Gly77Ser) which is a founder mutation in Saudi families, and a compound heterozygous mutation [(c.295delT; p.Phe99Leufs*18); (c.334A>G; p.Ser112Gly)] in 1 Italian family. An autosomal recessive inheritance pattern is suggested by the consanguinity reported in most cases. Therefore, the recurrence risk is 25% (n = 5) in each pregnancy. There is no clear genotype–phenotype correlation.

Diagnosis

Diagnosis can be established by DNA molecular genetic testing of the *ISCA2* gene.

Treatment

To date, no curative treatment has been discovered, and disease management is exclusively supportive. The management of *ISCA2* gene defects requires a multidisciplinary team approach including pediatricians, neurologists, geneticists, genetic counselors, dieticians, physiotherapists, and occupational therapists. Patients are at risk of gastroesophageal incoordination and swallowing difficulties which can lead to aspiration, malnutrition, and failure to thrive. In many patients, a feeding tube, such as gastrostomy tube, would be an efficient solution to ensure the patient receives sufficient calories and avoids recurrent aspirations. Additionally, periodic vision assessments are essential to have a clear knowledge about severity and progressive behavior of optic atrophy. Finally, regular follow-up visits with physiotherapists and occupational therapists are mandatory.

Prognosis

Multiple mitochondrial dysfunctions syndrome 4 as a result of the *ISCA2* gene defect is an apparently lethal disease and carries a poor prognosis. Of the cases known, 60% died early in childhood. The remainder had severe global developmental delay. The assumption of the lethality of this disease is limited by the small sample size (of 20 cases).

Conclusion

Clinicians should consider *ISCA2* gene defects as a diagnosis for any patient with the triad of neurodevelopmental regression, optic atrophy with nystagmus, and diffuse white matter disease. Additional case series will increase our knowledge of the severe clinical presentation, complications, and proper management of the disease.

Authors' contribution

M.A. contributed to conception and design; acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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Ethical Approval

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References

1. Chinnery PF. *Mitochondrial Disorders Overview*. Seattle, WA: University of Washington; 1993-2018.
2. Kirkman MA, Yu-Wai-Man P, Chinnery PF. The clinical spectrum of mitochondrial genetic disorders. *Clin Med (Lond)*. 2008; 8(6):601-606.
3. Vögtle FN, Brändl B, Larson A, et al. Mutations in PMPCB encoding the catalytic subunit of the mitochondrial presequence protease cause neurodegeneration in early childhood. *Am J Hum Genet*. 2018;102(4):557-573.
4. Seyda A, Newbold RF, Hudson TJ, et al. A novel syndrome affecting multiple mitochondrial functions, located by microcell-mediated transfer to chromosome 2p14-2p13. *Am J Hum Genet*. 2001;68(2):386-396.
5. Cameron JM, Janer A, Levandovskiy V, et al. Mutations in iron-sulfur cluster scaffold genes NFU1 and BOLA3 cause a fatal deficiency of multiple respiratory chain and 2-oxoacid dehydrogenase enzymes. *Am J Hum Genet*. 2011;89(4):486-495.
6. Ajit Bolar N, Vanlander AV, Wilbrecht C, et al. Mutation of the iron-sulfur cluster assembly gene IBA57 causes severe myopathy and encephalopathy. *Hum Mol Genet*. 2013;22(13):2590-2602.
7. Al-Hassnan ZN, Al-Dosary M, Alfadhel M, et al. ISCA2 mutation causes infantile neurodegenerative mitochondrial disorder. *J Med Genet*. 2015;52(3):186-194.
8. Alfadhel M, Nashabat M, Alrifai MT, et al. Further delineation of the phenotypic spectrum of ISCA2 defect: a report of ten new cases. *Eur J Paediatr Neurol*. 2018;22(1):46-55.
9. Shukla A, Hebbar M, Srivastava A, et al. Homozygous p. (Glu87Lys) variant in ISCA1 is associated with a multiple mitochondrial dysfunctions syndrome. *J Hum Genet*. 2017;62(7): 723-727.
10. Toldo I, Nosadini M, Boscardin C, et al. Neonatal mitochondrial leukoencephalopathy with brain and spinal involvement and high lactate: expanding the phenotype of ISCA2 gene mutations. *Metab Brain Dis*. 2018;33(3):805-812.
11. Alaimo JT, Besse A, Alston CL, et al. Loss-of-function mutations in ISCA2 disrupt 4Fe-4 S cluster machinery and cause a fatal leukodystrophy with hyperglycinemia and mtDNA depletion. *Hum Mutat*. 2018;39(4):537-549.
12. Alazami AM, Patel N, Shamseldin HE, et al. Accelerating novel candidate gene discovery in neurogenetic disorders via whole-exome sequencing of prescreened multiplex consanguineous families. *Cell Rep*. 2015;10(2):148-161.
13. Lill R, Diekert K, Kaut A, et al. The essential role of mitochondria in the biogenesis of cellular iron-sulfur proteins. *Biol Chem*. 1999; 380(10):1157-1166.
14. Kispal G, Csere P, Prohl C, Lill R. The mitochondrial proteins Atm1p and Nfs1p are essential for biogenesis of cytosolic Fe/S proteins. *EMBO J*. 1999;18(14):3981-3989.
15. Netz DJ, Mascarenhas J, Stehling O, Pierik AJ, Lill R. Maturation of cytosolic and nuclear iron-sulfur proteins. *Trends Cell Biol*. 2014;24(5):303-312.
16. Lill R. Function and biogenesis of iron-sulphur proteins. *Nature*. 2009;460(7257):831-838.
17. Sheftel AD, Wilbrecht C, Stehling O, et al. The human mitochondrial ISCA1, ISCA2, and IBA57 proteins are required for [4Fe-4S] protein maturation. *Mol Biol Cell*. 2012;23(7): 1157-1166.
18. Alfadhel M, Nashabat M, Abu Ali Q, Hundallah K. Mitochondrial iron–sulfur cluster biogenesis from molecular understanding to clinical disease. *Neurosciences (Riyadh)*. 2017;22(1): 4-13.
19. Beilschmidt LK, Ollagnier de Choudens S, Fournier M, et al. ISCA1 is essential for mitochondrial Fe4S4 biogenesis in vivo. *Nat Commun*. 2017;8:15124.
20. Gourdoupis S, Nasta V, Calderone V, Ciofi-Baffoni S, Banci L. IBA57 Recruits ISCA2 to Form a [2Fe-2 S] cluster-mediated complex. *J Am Chem Soc*. 2018;140(43):14401-14412.
21. Navarro-Sastre A, Tort F, Stehling O, et al. A fatal mitochondrial disease is associated with defective NFU1 function in the maturation of a subset of mitochondrial Fe-S proteins. *Am J Hum Genet*. 2011;89(5):656-667.
22. Al-Hassnan ZN, Kaya N. ISCA2-related mitochondrial disorder. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, et al. eds. *GeneReviews*. Seattle, WA: The University of Washington; 1993-2018.