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A Case of Multiple Mitochondrial Dysfunctions Syndrome 4 with Novel *ISCA2* Variants, Mimicking Post-Infectious Encephalitis

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Abstract

ISCA2 loss of function leads to leukodystrophy and developmental regression (multiple mitochondrial dysfunctions syndrome 4 (MMDS4)). We present a first Korean case of MMDS4 presenting with rapid developmental regression and leukodystrophy after febrile episode, mimicking post-infectious encephalitis. The patient had displayed normal development until 12 months of age. At 13 months of age, one month after experiencing a post-vaccination fever, she quickly progressed to being unable to sit unassisted nor speak any words. Analysis of the cerebrospinal fluid (CSF) revealed lympho-dominant pleocytosis. Amino acid analysis of both the serum and CSF demonstrated elevated glycine exclusively in the CSF. Diffuse leukodystrophy was noted in the brain magnetic resonance image. Whole exome sequencing revealed compound heterozygous *ISCA2* variants of c.166T>G, p.C56G and c.422A>C, p.Q141P. No evidence of mitochondrial disease other than bilateral optic atrophy was noted. In cases of early onset rapid developmental regression with leukodystrophy, MMDS4 should be considered.

Keywords

ISCA2, multiple mitochondrial dysfunctions syndrome 4, developmental regression, leukodystrophy, glycine

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Introduction

Iron sulfur cluster (ISC) is an essential inorganic cofactor. [4Fe-4S] cluster constitutes mitochondrial respiratory chain complex I and II,[1] and is a cofactor of lipoic acid synthase, whose product lipoic acid is a cofactor of the H subunit of the glycine cleavage system and mitochondrial ketoacid dehydrogenase complexes.[2] ISC biogenesis starts in the mitochondria, and maturation is regulated by *NFU1, BOLA3, IBA57, ISCA2,* and *ISCA1,*[2–4] whose loss of function variants are known to cause multiple mitochondrial dysfunctions syndrome (MMDS). *ISCA2* loss of function leads to MMDS4, characterized by infantile onset developmental regression often rapidly progressing to vegetative state or death with neuroimaging findings of diffuse leukodystrophy. Twenty-four cases of MMDS4, and four homozygous and two compound heterozygous *ISCA2* variants have been reported to date.[1–8]

Here we present a case of novel compound heterozygous *ISCA2* variant, in a 13 months old girl presenting with acute developmental regression after a febrile illness, mimicking post-infectious encephalitis.

Case

A 13 months old girl presented to our hospital with developmental regression. She was born uneventfully at 40 weeks of gestational age with a birth weight of 3700 grams. She showed normal development until 12 months of age, being able to walk with one hand held, grasping objects with two fingers, and speaking a couple of meaningful words. Her family history was unremarkable.

One month prior to her hospital visit, the patient experienced fever lasting for three days following inactivated Japanese

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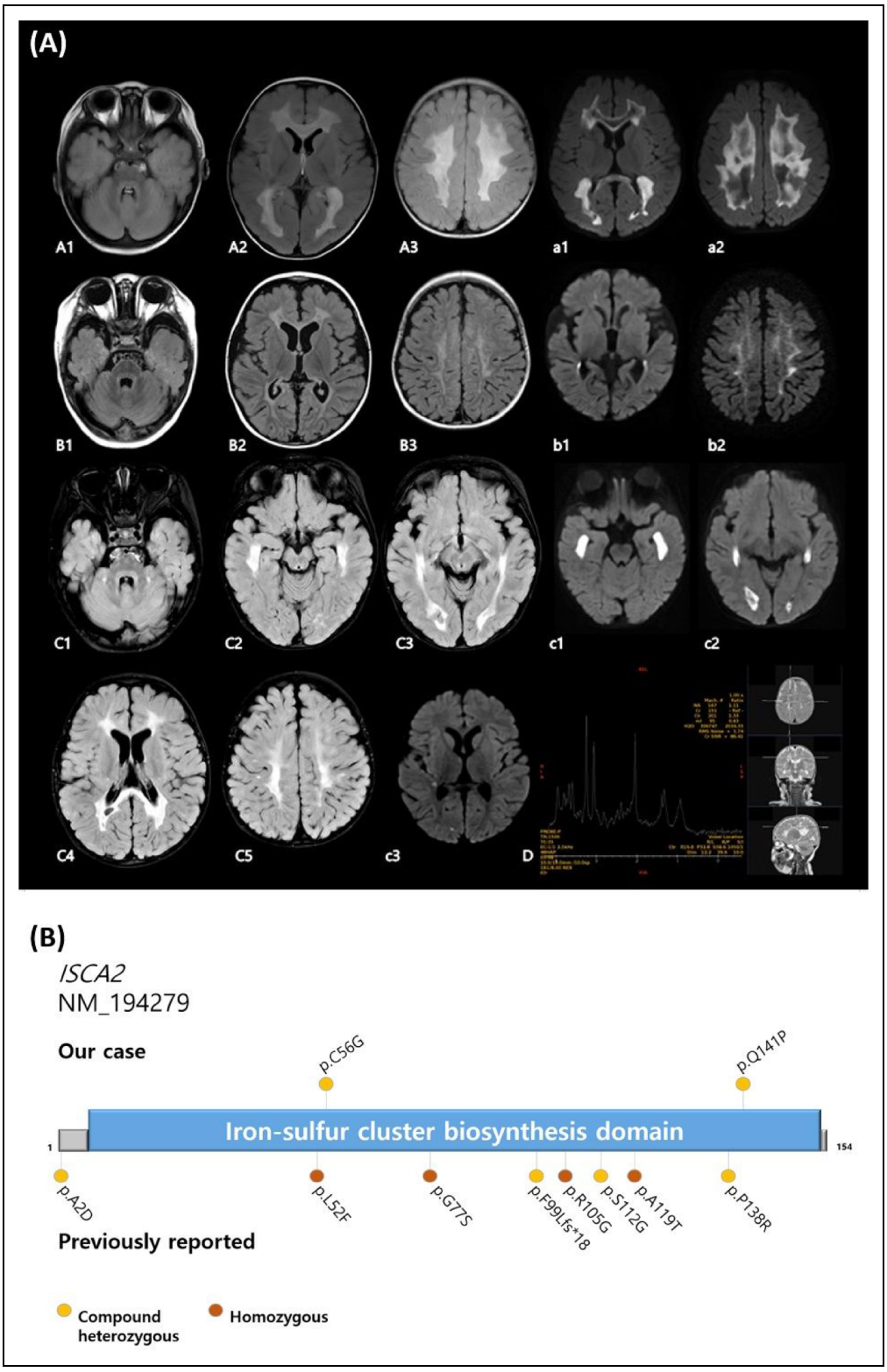

Figure 1. A. Temporal changes of brain magnetic resonance image. (A, B, C) Fluid attenuated inversion recovery image. (a, b, c) Diffusion weighted image. (A, a) At initial presentation of 13 months of age. Bilateral leukodystrophy with diffusion restriction is found, involving corpus callosum. (B, b) At 16 months of age, after corticosteroid therapy, the extent of leukodystrophy and diffusion restriction improved. Interval atrophic change of brain is noted. (C, c) At 19 months of age, after genetic diagnosis, aggravated leukodystrophy extending to subcortical white matter, with subependymal cystic changes and diffusion restriction is shown. (D) Spectroscopy at 19 months of age shows no increase in lactate peak. **B.** Pathogenic *ISCA2* variants reported to date (Reference sequence NM_194279). Homozygous variants are colored as brown, and compound heterozygous variants are colored as yellow.

Encephalitis and Hepatitis A vaccinations. Approximately two weeks after receiving the vaccinations, she could not walk and only stood with assistance. Additionally, her oral intake decreased, and she became increasingly irritable. At the time of presentation, she was unable to sit without support, unable to produce meaningful speech, and required nasogastric tube for feeding. Nystagmus was present with poor eye contact. Her extremities were spastic and bilateral ankle clonus was present upon neurological examination.

The laboratory results for the patient's complete blood cell count, liver function tests, renal function tests, and C-reactive protein level were all within normal ranges. Serum lactate levels were measured at 2.3 mmol/L. Analysis of the CSF showed lympho-dominant pleocytosis, without any notable increase in protein levels (red blood cell count: 0/μL, white blood cell count: 28/μL, lymphocyte count: 24/μL, protein level: 19 mg/dL, glucose level: 55 mg/dL). Microbiological studies of the CSF did not reveal any evidence of infection. Brain magnetic resonance imaging (MRI) showed leukodystrophy affecting the bilateral periventricular white matter (PVWM) and corpus callosum, while the subcortical white matter remained unaffected. Diffusion restriction was observed in

Table 1. Clinical Characteristics, Laboratory and Radiologic Findings of our Case and Previously Reported Cases of MMDS4.

	Previously reported cases of MMDS4 (n = 24)[1–5,7,8]	Our case (n = 1)
Inheritance	22 homozygous, 2 compound heterozygous	Compound heterozygous
Clinical characteristics		
Sex – female (%)	13 (54)	1
Age at onset – yrs, median (IQR)	0.4 (0.25-0.5)	1.1
Presenting symptoms	Developmental regression (motor, language, loss of fixation/ nystagmus), hypotonia, apnea, irritability, insomnia	Developmental regression, nystagmus
Optic atrophy – n	17	Yes
Seizure – n	4	No
Preceding febrile illness – n	2	Yes
Mortality – n (%)	13 (54)	No
Age at death – yrs, median (IQR)	1.1 (0.9-2.0)	
Age at last alive follow-up – yrs, median (IQR)	1.5 (1.1-3.3)	1.9
Documented improvement of any degree after symptom onset	1	Yes
Known consanguinity – n (%)	20 (83)	No
Neuroimaging findings		
Leukodystrophy – n (%)	23 (96)	Yes
PVWM – n	20	Yes
Corpus callosum – n	3	Yes
Internal capsule – n	5	No
Subcortical WM – n	2	Yes
Cerebellum – n	18	Yes
Brainstem – n	3	No
Spinal cord WM – n	11	
Cystic changes – n	1	Yes
MR Spectroscopy – n	8	Yes
Increased lactate peak – n	7	No
Increased glycine peak – n	2	
Laboratory findings		
Serum		
Lactate measured – n	14	Yes
Increased lactate – n	5 (highest 4.0 mmol/L)	No
Glycine measured – n	10	Yes
Increased glycine – n	3	No
Cerebrospinal fluid		
Lactate measured – n	8	No
Increased lactate – n	7 (highest 7.4 mmol/L)	
Glycine measured – n	3	Yes
Increased glycine – n	3 (highest 43 μM/L)	Yes (112 μM/L)
Management		
	One case with methylprednisolone pulse, One case with methylprednisolone pulse and IVIG	Methylprednisolone pulse and IVIG

the PVWM without any contrast enhancement. The levels of arylsulfatase A and beta-galactosidase activities were within normal limits.

Methylprednisolone pulse therapy was given with subsequent corticosteroid maintenance therapy. One month later, at 14 months of age, her oral swallowing was improved and nasogastric tube was removed. She could sit alone, and speak a few meaningful words again. Follow-up brain MRI taken after steroid therapy showed decreased areas of diffusion restriction and leukodystrophy. Steroid was tapered off during two cycles of intravenous immunoglobulin.

At 19 months of age, she walked with support, spoke few meaningful words, and could make eye contacts. Bayley scales of infant and toddler development were 10 months in gross motor scale, 8 months in fine motor scale, 9 months in receptive language and 12 months in expressive language scale, and 6 months in cognitive scale. Her developmental milestones reached a plateau and did not achieve further milestones at her last follow up in 23 months of age. Clinical overview of the described case is shown in supplementary figure and summary of brain MRI findings is shown in Figure 1A.

Whole exome sequencing revealed compound heterozygous *ISCA2* variants of c.166T>G, p.C56G and c.422A>C, p.Q141P, rare variants not found on Genome Aggregation Database and Korean Variant Archive 2,[9,10] each inherited from her parents. The variants were initially classified as variant of unknown significance based on ACMG/AMP (American College of Medical Genetics and Genomics / Association for Molecular Pathology) criteria. Amino acid analysis of the stored initial serum and CSF samples showed normal serum glycine level but markedly elevated CSF glycine (112 μM/L, reference range 2.9-7.9 μM/L), a typical biochemical findings consistent with *ISCA2*-related MMDS4. CSF lactate was not measured due to inadequate sample quantity. A follow up Brain MRI taken 6 months after symptom onset showed progressed leukodystrophy and cystic changes. Lactate was not increased in brain Magnetic Resonance Spectroscopy. Bilateral optic atrophy was present in ophthalmologic exam. Based on the matching clinical presentation and biochemical studies, we reclassified the variants as likely pathogenic variants and concluded that *ISCA2* variants were the genetic cause of her clinical manifestation.

Discussion

We present the first case of MMDS4 in Korean population with rare novel compound heterozygous *ISCA2* variants. Although the history of developmental regression after febrile illness, lympho-dominant CSF pleocytosis and initial brain MRI findings suggested of post-infectious encephalitis, unusually rapid deterioration of motor functions called for further investigation. Compound heterozygous *ISCA2* variants along with elevated CSF glycine level supported the diagnosis of MMDS4. There were two previously reported cases of MMDS4 with preceding febrile illness[4] both harboring p.G77S homozygous variant. Though MMDS4 is characterized by rapid motor function deteriorations and progressing leukodystrophy, febrile event may trigger the disease, making it difficult to diagnose at initial presentation. Our case of *ISCA2* related MMDS4 after febrile episode strongly adds on to increasing awareness of the disease phenotype mimicking post-infectious encephalitis. MMDS4 seems to have poor prognosis, with 13 of 24 previously reported cases expired at median age of 1.1 years. All reported patients presented before age 1 (Table 1).

All previously reported cases of MMDS4 which measured CSF glycine levels had elevated CSF glycine levels. Serum glycine was elevated mildly only in one case (330 μM/L, reference value 74 to 290 μM/L). They all harbored p.G77S homozygous variant. In our case, CSF glycine level was elevated to 112 μM/L with normal serum glycine levels. Glycine elevation in serum or CSF is characteristic finding of MMDS, possibly associated with lipoic acid synthase dysfunction and subsequent defective glycine cleavage system.[1]

Although immunomodulative therapies have been proven effect in some mitochondrial leukoencephalopathies,[11] there is currently no proven treatment for MMDS4. In a case who is still alive at 11 years of age with infantile onset and partially regained developmental milestones after initial regression, methylprednisolone pulse and IVIG was given at initial diagnosis but with no effect.[8] In another case of 2-month-old girl, methylprednisolone pulse was given but the patient soon expired due to respiratory failure.[5] Our patient showed improvement in oral intake after corticosteroid therapy, and gradually regained some developmental milestones over 6 months while continuing IVIG treatment. Due to conflicting effects of immunomodulative therapies, further investigations are needed to fully understand their effects. A recent study demonstrating reactive oxygen species (ROS) accumulation in *ISCA2* knockdown cells calls for further investigations in ROS scavenger treatment options.[12]

In this report, we present a case harboring *ISCA2* variants with acute developmental regression after a febrile illness. A comprehensive literature review and summary of all reported ISCA2 variants and their associated phenotypes has been conducted to enhance the understanding of the overall clinical characteristics of ISCA2-related MMDS4. In conclusion, MMDS4 should be considered in infantile developmental regression with leukodystrophy. Since MMDS4 can manifest with a preceding febrile illness and mimic post-infectious encephalitis, the measurement of CSF glycine levels can assist in the diagnostic process and serve as an indicator for additional genetic investigations.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval and Informed Consent

Ethical approval to report this case was obtained from the Institutional Review Board of Seoul National University Hospital (IRB No: 2204-112-1317). Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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Supplemental Material

Supplemental material for this article is available online.

References

1. Alaimo JT, Besse A, Alston CL, et al. Loss-of-function mutations in ISCA2 disrupt 4Fe-4S cluster machinery and cause a fatal leukodystrophy with hyperglycinemia and mtDNA depletion. *Hum Mutat.* 2018;39(4):537-549. doi:10.1002/humu.23396
2. Lebigot E, Gaignard P, Dorboz I, et al. Impact of mutations within the [Fe-S] cluster or the lipoic acid biosynthesis pathways on mitochondrial protein expression profiles in fibroblasts from patients. *Mol Genet Metab.* 2017;122(3):85-94. doi:10.1016/j.ymgme.2017.08.001
3. 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. doi:10.1136/jmedgenet-2014-102592
4. 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. doi:10.1016/j.ejpn.2017.10.003
5. 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. doi:10.1007/s11011-017-0181-3
6. 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. doi:10.1016/j.celrep.2014.12.015
7. Eidi M, Garshasbi M. A novel ISCA2 variant responsible for an early-onset neurodegenerative mitochondrial disorder: A case report of multiple mitochondrial dysfunctions syndrome 4. *BMC Neurol.* 2019;19(1):153. doi:10.1186/s12883-019-1387-2
8. Hartman TG, Yosovich K, Michaeli HG, et al. Expanding the genotype-phenotype spectrum of ISCA2-related multiple mitochondrial dysfunction syndrome-cavitating leukoencephalopathy and prolonged survival. *Neurogenetics*. 2020;21(4):243-249. doi:10.1007/s10048-020-00611-8
9. Lee J, Lee J, Jeon S, et al. A database of 5305 healthy Korean individuals reveals genetic and clinical implications for an East Asian population. *Exp Mol Med.* 2022;54(11):1862-1871. doi:10.1038/s12276-022-00871-4
10. Chen S, Francioli LC, Goodrich JK, et al. A genome-wide mutational constraint map quantified from variation in 76,156 human genomes. *bioRxiv*. 2022:2022.03.20.485034. doi:10.1101/2022.03.20.485034
11. Bindu PS, Sonam K, Chiplunkar S, et al. Mitochondrial leukoencephalopathies: A border zone between acquired and inherited white matter disorders in children? *Mult Scler Relat Disord*. 2018;20:84-92. doi:10.1016/j.msard.2018.01.003
12. Wang J, Jiang M, Yue G, et al. ISCA2 Deficiency leads to heme synthesis defects and impaired erythroid differentiation in K562 cells by indirect ROS-mediated IRP1 activation. *Biochim Biophys Acta Mol Cell Res*. 2022;1869(10):119307. doi:10.1016/j.bbamcr.2022.119307