

LETTER TO EDITOR

Autism spectrum disorder: A mitochondrial disorder

How to Cite This Article: Finsterer J^{ID}. Autism spectrum disorder: A mitochondrial disorder. *Iran J Child Neurol.* Autumn 2021; 15(4): 115-117

Josef FINSTERER MD¹

1. Messerli Institute, Klinik
Landstrasse, Vienna, Austria

Corresponding Author

Finsterer j. MD
Messerli Institute, Klinik
Landstrasse, Vienna, Austria
Email: fipaps@yahoo.de

Received: 30-Nov- 2020

Accepted: 28-Apr-2021

Letter to the Editor

With interest, we read the review article by Ahmadabadi et al. on autism spectrum disorders (ASDs) in inborn errors of metabolism (IEM) (1). They reviewed 37 studies, and found that IEMs underlie autistic features in <5% of the patients, and that there is growing evidence on the association between ASDs and mitochondrial disorders (MIDs), including mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS) syndrome, and respiratory chain complex III/IV deficiency (1). The authors concluded that the syndromic autism, a strong family history, or consanguinity suggest IEM (1). However, we have raised the following comments and concerns:

We disagree with the idea that mitochondrial disorders (MIDs) have only two points of onset as they can occur at any age, and their broad variability, even in a family, results from the peculiarities of mitochondrial genetics. Due to mutations in mtDNA-located genes, MIDs are maternally transmitted, and the underlying mtDNA mutations may not occur in each mtDNA copy (heteroplasmy). Moreover, mtDNA copy number may considerably vary from one mitochondrion to another mitochondrion, particularly if the mutation is located in a nuclear-encoded gene. MIDs frequently manifest in the central nervous system (CNS), and the CNS manifestations may include psychiatric or neurological diseases or both. The psychiatric diseases range from mild cognitive impairment and personality change to delirium and psychosis. Autism has been frequently reported in MIDs (2) and may or may not be associated with cerebral morphological alterations.

We also disagree that ASD occurs only in MELAS and complex-III/IV deficiency (1). ASD has also been reported in a patient carrying the mtDNA variant m.8363G>A, whose sister was carrying the same variant and presented with Leigh syndrome (3), as well as in two

Autism spectrum disorder: A mitochondrial disorder

Korean siblings carrying the variant c.790C>T in TFB2M (4). In a study on 60 ASD patients, single mtDNA deletions were detected in 16.6% of the patients (5). In the same study, the ten patients with mtDNA deletions also carried single nucleotide variants (SNVs) in ASD-associated genes (5). In a study on 95 ASD patients, the mtDNA content decreased in the ASD patients, and 49 putative pathogenic mtDNA variants were detected (6). In a study on 10 families with ASD, whole-exome sequencing revealed the variants of interest (VOIs) in the ND5 gene in one family and VOIs in ATP6 and NDUFS4 in another family (7). In a study on 24 Iranian ASD patients, mtDNA mutations 16126T>C, m.14569G>A, and m.,1811A>G, all of which were located in non-coding regions, showed a significant relationship with ASD (8).

In general, there is ample evidence indicating that the IEM, which is most frequently associated with ASD, is MID. According to the literature, the mtDNA variants but not the nDNA variants have been more frequently associated with ASD. Patients with an ASD should be first examined in terms of the presence or absence of MID.

Keywords: MTDNA; Mitochondrial; Respiratory Chain; Autism; Abnormal behaviour

DOI:10.22037/ijcn.v16i2.33066

Acknowledgement

None

Authors' Contribution

Finsterer J, Research design, literature review, discussion, first draft, critical comments

Informed consent: The participants' informed consent was received.

The study was approved by the Institutional Review Board.

Conflict of interest

The authors declare no conflict of interest.

References

1. Ahmadabadi F, Nemati H, Abdolmohammadzadeh A, Ahadi A. Autistic feature as a presentation of Inborn Errors of Metabolism. *Iran J Child Neurol*. 2020 Fall;14(4):17-28.
2. Connolly BS, Feigenbaum AS, Robinson BH, Dipchand AI, Simon DK, Tarnopolsky MA. MELAS syndrome, cardiomyopathy, rhabdomyolysis, and autism associated with the A3260G mitochondrial DNA mutation. *Biochem Biophys Res Commun*. 2010 Nov 12;402(2):443-7. doi: 10.1016/j.bbrc.2010.10.060.
3. Graf WD, Marin-Garcia J, Gao HG, Pizzo S, Naviaux RK, Markusic D, Barshop BA, Courchesne E, Haas RH. Autism associated with the mitochondrial DNA G8363A transfer RNA(Lys) mutation. *J Child Neurol*. 2000 Jun;15(6):357-61. doi: 10.1177/088307380001500601. .
4. Park CB, Choi VN, Jun JB, Kim JH, Lee Y, Lee J, Lim G, Kim J, Jeong SY, Yim SY. Identification of a rare homozygous c.790C>T variation in the TFB2M gene in Korean patients with autism spectrum disorder. *Biochem Biophys Res Commun*. 2018 Dec 9;507(1-4):148-154. doi: 10.1016/j.bbrc.2018.10.194.
5. Varga NÁ, Pentelényi K, Balicza P, Gézsi A, Reményi V, Hársfalvi V, Bencsik R, Illés A, Prekop C, Molnár MJ. Mitochondrial dysfunction and autism: comprehensive genetic analyses of children with autism and mtDNA deletion. *Behav Brain Funct*. 2018 Feb 20;14(1):4. doi: 10.1186/s12993-018-0135-x. PMID: 29458409; PMCID: PMC5819172.
6. Valiente-Pallejà A, Torrell H, Muntané G, Cortés MJ, Martínez-Leal R, Abasolo N, Alonso Y,

Autism spectrum disorder: A mitochondrial disorder

- Vilella E, Martorell L. Genetic and clinical evidence of mitochondrial dysfunction in autism spectrum disorder and intellectual disability. *Hum Mol Genet.* 2018 Mar 1;27(5):891-900. doi: 10.1093/hmg/ddy009.
7. Patowary A, Nesbitt R, Archer M, Bernier R, Brkanac Z. Next Generation Sequencing Mitochondrial DNA Analysis in Autism Spectrum Disorder. *Autism Res.* 2017 Aug;10(8):1338-1343. doi: 10.1002/aur.1792.
8. Mousavizadeh K, Askari M, Arian H, Gourjipour F, Nikpour AR, Tavafjadid M, Aryani O, Kamalidehghan B, Maroof HR, Houshmand M. Association of human mtDNA mutations with autism in Iranian patients. *J Res Med Sci.* 2013 Oct;18(10):926.