Received: 7 May 2023 | Revised: 3 June 2023 | Accepted: 7 June 2023

DOI: 10.1002/ccr3.7592

Clinical Case Reports Open Access WILEY

CASE REPORT

Effective treatment of choreaballism due to an *MT-CYB* variant with haloperidol, tetrabenazine, and antioxidants

Josef Finsterer[1] | **Ritwik Ghosh**[2]

[1]Neurology & Neurophysiology Center, Vienna, Austria

[2]Department of General Medicine, Burdwan Medical College & Hospital, Burdwan, West Bengal, India

Correspondence
Josef Finsterer, Neurology & Neurophysiology Center, Postfach 20, 1180 Vienna, Austria.
Email: fipaps@yahoo.de

Key Clinical Message

Hypokinetic and hyperkinetic movement disorders are a common phenotypic feature of mitochondrial disorders. Choreaballism has been reported particularly in patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome and in maternally inherited diabetes and deafness syndrome. The pathophysiological basis of movement disorders in mitochondrial disorders is the involvement of the basal ganglia or the midbrain. Haloperidol and mitochondrial cocktails have proven beneficial in some of these cases. Here we present another patient with mitochondrial choreaballism who benefited significantly from symptomatic therapy. The patient is a 14-year-old male with a history of hypoacusis, ptosis, and focal tonic–clonic seizures of the upper/lower limbs on either side since childhood. Since this time he has also developed occasional, abnormal involuntary limb movements, choreaballism, facial grimacing, carpopedal spasms, and abnormal lip sensations. He was diagnosed with a non-syndromic mitochondrial disorder after detection of the variant m.15043G > A in *MT-CYB*. Seizures have been successfully treated with lamotrigine. Hypocalcemia was treated with intravenous calcium. For hypoparathyroidism calcitriol was given. Choreaballism was treated with haloperidol and tetrabenazine. In addition, he received coenzyme Q10, L-carnitine, thiamine, riboflavin, alpha-lipoic acid, biotin, vitamin-C, vitamin-E, and creatine-monohydrate. With this therapy, the choreaballism disappeared completely. This case shows that mitochondrial disorders can manifest with cognitive impairment, seizures, movement disorder, hypoacusis, endocrinopathy, cardiomyopathy, neuropathy, and myopathy, that choreaballism can be a phenotypic feature of multisystem mitochondrial disorders, and that choreaballism favorably responds to haloperidol, tetrabenazine, and possibly to a cocktail of antioxidants, cofactors, and vitamins.

KEYWORDS

hereditary, hypoparathyroidism, lactic acidosis, mitochondrial, movement disorder, mtDNA, multisystem disease

Name of dpt. where work has been done: Neurology & Neurophysiology Center, Vienna.

1 | INTRODUCTION

Hypokinetic and hyperkinetic movement disorders are a common phenotypic feature of mitochondrial disorders (MIDs).[1] Parkinson's disease has been reported in a patient carrying the myoclonic epilepsy with ragged red fibers (MERRF) mtDNA mutation m.8344A > G.[2] Dystonia has been reported in Leigh syndrome and in Leber's hereditary optic neuropathy (LHON) plus.[3] Myoclonus is a canonical phenotypic feature of MERRF syndrome.[4] Choreaballism has been particularly reported in patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome and in maternally inherited diabetes and deafness (MIDD) syndrome.[5–7] In a nationwide Italian survey of 764 patients with MID, a movement disorder was found in 13.7% of patients.[8] In a cross-sectional survey of 102 children with MID from Italy, a movement disorder was the presenting phenotypic feature in 45 individuals with an average age of 11 years.[9] The most common movement disorder in this cohort was ataxia (actually not classified as such by the International Movement disorder Society) followed by dystonia, tremor, hypokinetic disorders, chorea, and myoclonus.[9] The pathophysiological basis of movement disorders in MIDs is an affection of the basal ganglia or the midbrain. In a patient with severe dystonia due to the homoplasmic variant m.3697G > A bilateral necrosis of the striatum was found on cerebral imaging.[10] Haloperidol and mitochondrial cocktails have been reported beneficial in some cases with choreaballism.[5,6] Here we present a single patient with mitochondrial choreaballism who profited with regard to choreaballism significantly from symptomatic therapy. The patient underwent routine, clinical investigations, including routine blood tests, cerebrospinal fluid (CSF) investigations, electroencephalography (EEG), cerebral computed tomography (CCT), cerebral magnetic resonance imaging (MRI), needle electromyography (EMG), nerve conduction studies (NCSs), electrocardiography (ECG), and genetic work-up.

2 | CASE REPORT

The patient is a 14-year-old Indian male, height 147 cm, weight 40 kg, who was admitted because of a generalized tonic–clonic seizure. His history was positive for hypoacusis, ptosis, and focal tonic–clonic seizures of the upper and lower limbs on either side since childhood. For focal seizures he did not receive any anti-seizure drugs (ASDs). The family history was negative for mitochondrial disorders. The parents were non-consanguineous. At the age of 14 mild quadruparesis developed. Thereafter, focal seizures were followed by generalized seizures, occasionally complicated by postictal hemiparesis (Todd paresis). In addition, the patient developed occasional, abnormal involuntary movements of limbs, choreaballism with left-sided predominance, facial grimacing, carpopedal spasms, and abnormal sensations of the lips.

Neurologic exam revealed mild cognitive impairment, hypoacusis, ptosis, proximal weakness of upper and lower limbs (muscle research council [MRC] grade 4), absent deep tendon reflexes, and positive Chvostek and Trousseaus' signs. Further work-up by blood tests revealed hypocalcemia, hyperphosphatemia, hypoparathyroidism, elevated creatine-kinase, and lactic acidosis (Table 1). CSF lactate was elevated to 37.3 mg/dL [RI 13.7–20.5 mg/dL]. The EEG was free of epileptiform discharges. The CCT revealed bilateral calcifications of the putamen and calcifications periventricularly (Figure 1). Cerebral MRI showed bilateral, non-enhancing, T1- and susceptibility-weighted imaging (SWI) hyperintensities of the basal ganglia and periventricularly. NCSs revealed mild axonal neuropathy of the tibial and peroneal nerves. Needle EMG was myogenic. ECG showed T-wave flattening and QT-prolongation. Transthoracic echocardiography revealed mild myocardial thickening and mild diastolic dysfunction.

Genetic work-up for a suspected MID revealed the variant m.15043G > A in *MT-CYB*. Seizures were successfully treated with lamotrigine (100 mg per day) since admission. Hypocalcemia was substituted with calcium intravenously. For hypoparathyroidism calcitriol (0.25 µg per day) was given. Choreaballism was treated with haloperidol (1 mg per day) and tetrabenazine (25 mg per day) since hospital Day 4. For the mitochondrial disorder a cocktail comprising coenzyme Q10 (75 mg per day), L-carnitine (1000 mg per day), thiamine (200 mg per day), riboflavin (20 mg per day), alpha lipoic acid (600 mg per day), biotin (20 mg per day), vitamin-C (1000 mg per day), vitamin-E (400 mg per day), and creatine monohydrate (10 mg per day) was given after genetic confirmation of the MID. At follow-up, 8 months after starting the treatment,

TABLE 1 Abnormal results of blood and CSF tests obtained during the most recent hospitalization.

	Reference limits	Patient
Ionized calcium	1.1–1.35 mmol/L	0.86 mmol/L
Total calcium	8.5–10.l mg/dL	5 mg/dL
Phosphorus	2.9–5.1 mg/dL	26.1 mg/dL
Parathormone	8.7–79-6 pg/mL	6.2 pg/mL
Serum lactate	0.5–1.0 mmol/L	8.28 mmol/L
Pyruvate	0.030–0.107 mmol/L	0.134 mmol/L
Arterial pH	7.28–7.32	7.12
CSF lactate	13.7–20.5 mg/dL	37.3 mg/dL

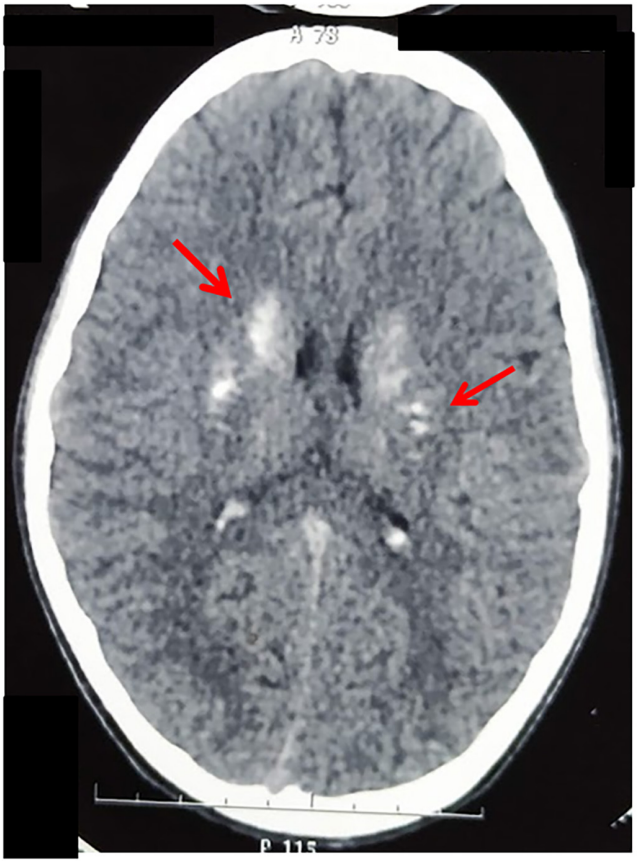

FIGURE 1 Cerebral CT scan without contrast medium of the index patient at age 14 y showing bilateral calcification of the putamen and calcifications periventricularly.

choreaballism had completely resolved. The patient was seizure-free. The quadruparesis had resolved. The tendon reflexes showed a tendency to recover. Only ptosis and slight cognitive deficits persisted.

3 | DISCUSSION

The presented case shows that MIDs can manifest with cognitive impairment, seizures, movement disorders, hypoacusis, endocrinopathy, cardiomyopathy, neuropathy, and myopathy. The multisystem character of MIDs is a common finding,[11] which often only becomes apparent as the disease progresses. The organs or systems most commonly affected in MIDs are the skeletal muscle, the central nervous system, and the endocrine system.[11] Movement disorders are an increasingly recognized central nervous system (CNS) manifestation of MIDs.[12] In the index patient, movement disorder manifested as choreaballism, which was attributed to affection of the basal ganglia. Although the extent of the calcifications on the CCT was smaller than the extent of the T1-lesions on the MRI, a causal relationship was suspected. Hyperparathyroidism alone has not been considered to be the cause of the basal ganglia calcifications. The reason why choreaballism occurred with left-sided predominance remains speculative, but could be attributed to the asymmetry of the basal ganglia calcifications or the T1-lesions.

Whether the variant m.15043G > A was really causal remains speculative, since conflicting results regarding the pathogenicity of this variant have been reported.[13,14] On MITOMAP the mtDNA variant m.15043G > A is described to perturb the activity of cytochrome B1 and reported to be pathogenic.[15] In a study of three female patients with a MID from China, one patient carried the mtDNA variants m.16183A > C, m.16189T > C, and n.15043G > A in the D-loop.[16] It was not specified which of these variants was the cause. Biochemical investigations of the muscle homogenate revealed isolated complex-I deficiency.[16] Phenotypically, the patient presented with cardiomyopathy complicated by ventricular arrhythmias, slight systolic dysfunction, and elevated creatine-kinase-MB fraction.[16] The patient additionally presented with myopathy, manifesting as hyper-creatine-kinase emia.[16] In a study of 77 patients with schizophrenia, bipolar disorder, or major depressive disorder, the variant m.15043G > A was detected in 15 patients with the M, N, and pre HV haplogroup.[17] A causal relation between the variant and the psychiatric disease was discussed but remained unproven.[17] In a study of seven patients with atypical psychosis, the variant m.15043G > A was detected in two of them without the finding being discussed further.[18] In a study of 250 Korean patients with non-small-cell lung cancer, the variant m.15043G > A was detected in the tumor tissue by sequencing the entire mrDNA and was considered to be one of the causes.[19] In a Tunisian study with 40 patients with dilated cardiomyopathy and 30 patients with hypertrophic cardiomyopathy, mtDNA sequencing revealed the variant m.15043G > A in one patient each with dilated and hypertrophic cardiomyopathy.[20] The variant was classified as a nonpathogenic polymorphism in this study.[19] In a study of 34 patients with aggressive periodontitis the variant m.15043G > A was detected as one of eight mtDNA polymorphisms associated with the dental disorder.[21]

Interestingly, choreaballism in the index patient responded favorably to haloperidol, tetrabenazine, and possibly to the cocktail of antioxidants, cofactors, and vitamins. Generally, treatment of choreaballism depends on the underlying cause. In Huntington's disease chorea responds favorably to the vesicular monoamine transporter type 2 inhibitors deu-tetrabenazine or tetrabenazine.[22] If chorea is part of a tardive dyskinesia syndrome, valbenazine and deu-tetrabenazine are usually considered.[23] If treatment with L-DOPA is the cause of chorea, treatment with amantadine has proven itself.[24] Antipsychotics can be considered if chorea occurs together with psychiatric conditions,

such as agitation, irritability, anxiety, depression, suicidal ideation, or apathy. In children with severe Sydenham's chorea, improvement can be achieved with the use of corticosteroids in combination with antibiotics to treat the rheumatic infection with beta-hemolytic Streptococcus.[25] Chorea due to endocrine or metabolic disorders, such as hyperthyroidism, hypoglycemia, hypoparathyroidism, hypocalcemia, or hypomagnesemia, responds most favorably to treatment of the underlying condition.[26,27] A nondrug treatment for chorea is deep brain stimulation (DBS). It has been successfully applied in patients with Huntington's chorea,[28] in patients with chorea due to acanthocytosis,[29] or in patients with chorea due to cerebral hypoxia.[30] As most of the drugs mentioned above have side effects, it is crucial to weigh the risk and benefit for the patient and to stop the drug, even if it is beneficial. Side effects particularly occur with tetrabenazine (suicidal thoughts), steroids (metabolic myopathy, hypertension, diabetes, osteoporosis, etc.), amantadine (hallucinations), or antipsychotics (Parkinson syndrome, tardive dyskinesias, and QT-prolonogation).

Limitations of the study were that no muscle biopsy was performed to look for immune-histological features of MID, the pathogenicity of the variant in the *MT-CYB* gene was not substantiated by functional or cybrid studies, no biochemical investigations were performed, that the patient has not been systematically evaluated for multisystem involvement, and that first-degree relatives have not been systematically evaluated clinically and genetically.

4 | CONCLUSIONS

This case shows that certain non-syndromic MIDs manifest with cognitive impairment, seizures, movement disorders, hypoacusis, endocrinopathy, cardiomyopathy, neuropathy, myopathy, that choreaballism can be a phenotypic feature of a multisystem MID, and that choreaballism can favorably respond to haloperidol, tetrabenazine, and possibly to a cocktail of antioxidants, cofactors, and vitamins.

AUTHOR CONTRIBUTIONS

Josef Finsterer: Formal analysis; methodology; resources; validation; writing – original draft. **Ritwik Ghosh:** Data curation; formal analysis; validation; visualization.

FUNDING INFORMATION

No funding was received.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

All data are available from the corresponding author.

ETHICS STATEMENT

The research has been given ethical approval.

CONSENT STATEMENT

Written informed consent was obtained from the parents of the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Josef Finsterer https://orcid.org/0000-0003-2839-7305
Ritwik Ghosh https://orcid.org/0000-0002-8192-0807

REFERENCES

1. Finsterer J, Zarrouk-Mahjoub S. Spectrum of movement disorders in mitochondrial disorders. *JAMA Neurology*. 2016;73:1253-1254.
2. Horvath R, Kley RA, Lochmüller H, Vorgerd M. Parkinson syndrome, neuropathy, and myopathy caused by the mutation A8344G (MERRF) in tRNALys. *Neurology*. 2007;68(1):56-58. doi:10.1212/01.wnl.0000250334.48038.7a
3. Berardo A, Emmanuele V, Vargas W, Tanji K, Naini A, Hirano M. Leber hereditary optic neuropathy plus dystonia, and transverse myelitis due to double mutations in MT-ND4 and MT-ND6. *Journal of Neurology*. 2020;267(3):823-829. doi:10.1007/s00415-019-09619-z
4. Hameed S, Tadi P. Myoclonic epilepsy and ragged red fibers. *StatPearls [Internet]*. StatPearls Publishing; 2021.
5. Ko TH, Lee HH, Hsieh AT, Hu CJ, Chen CC. Bilateral choreaballism and diabetic ketoacidosis as the initial presentation of a case with maternally inherited diabetes and deafness. *Acta Diabetologica*. 2017;54:795-797.
6. Lahiri D, Sawale VM, Banerjee S, Dubey S, Roy BK, Das SK. Chorea-ballism as a dominant clinical manifestation in heteroplasmic mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome with A3251G mutation in mitochondrial genome: a case report. *Journal of Medical Case Reports*. 2019;13(1):63. doi:10.1186/s13256-018-1936-0
7. Nakagaki H, Furuya J, Santa Y, Nagano S, Araki E, Yamada T. A case of MELAS presenting juvenileonset hyperglycemic chorea-ballism. *Rinshō Shinkeigaku*. 2005;45:502-505.
8. Montano V, Orsucci D, Carelli V, et al. Adult-onset mitochondrial movement disorders: a national picture from the Italian network. *Journal of Neurology*. 2021;269:1413-1421. doi:10.1007/s00415-021-10697-1
9. Ticci C, Orsucci D, Ardissone A, et al. Movement disorders in children with a mitochondrial disease: a cross-sectional survey from the Nationwide Italian collaborative network of mitochondrial diseases. *Journal of Clinical Medicine*. 2021;10(10):2063. doi:10.3390/jcm10102063
10. Zhong S, Wen S, Qiu Y, et al. Bilateral striatal necrosis due to homoplasmic mitochondrial 3697G>a mutation presents with incomplete penetrance and sex bias. *Molecular Genetics & Genomic Medicine*. 2019;7(3):e541. doi:10.1002/mgg3.541

11. Finsterer J. Clinical perspectives of mitochondrial disorders. *Pediatric Endocrinology Reviews*. 2018;16(1):203-208. doi:10.17458/per.vol16.2018.f.mitochondrialdisorders
12. Tranchant C, Anheim M. Movement disorders in mitochondrial diseases. *Revue Neurologique (Paris)*. 2016;172(8-9):524-529. doi:10.1016/j.neurol.2016.07.003
13. Alston CL, Blakely EL, McFarland R, Taylor RW. The m.15043G > a MT-CYB variant is not a pathogenic mtDNA variant. *Journal of the Neurological Sciences*. 2020;417:116950. doi:10.1016/j.jns.2020.116950
14. Ghosh R, Dubey S, Chatterjee S, et al. Pathogenicity of the m.15043G>a variant. *Journal of the Neurological Sciences*. 2020;417:116947. doi:10.1016/j.jns.2020.116947
15. MITOMAP. Reported Mitochondrial DNA Base Substitution Diseases: Coding and Control Region Point Mutations. Available from: https://www.mitomap.org/foswiki/bin/view/MITOMAP/MutationsCodingControl [Accessed August 8th, 2021]
16. Ma YY, Wu TF, Liu YP, et al. Clinical, biochemical and genetic analysis of the mitochondrial disorders presenting with cardiac damage. *Zhonghua Er Ke Za Zhi*. 2013;51(12):909-914.
17. Rollins B, Martin MV, Sequeira PA, et al. Mitochondrial variants in schizophrenia, bipolar disorder, and major depressive disorder. *PLoS One*. 2009;4(3):e4913. doi:10.1371/journal.pone.0004913
18. Kazuno AA, Munakata K, Mori K, et al. Mitochondrial DNA sequence analysis of patients with 'atypical psychosis'. *Psychiatry and Clinical Neurosciences*. 2005;59(4):497-503. doi:10.1111/j.1440-1819.2005.01404.x
19. Wang Z, Choi S, Lee J, et al. Mitochondrial variations in non-small cell lung cancer (NSCLC) survival. *Cancer Informatics*. 2015;14(Suppl 1):1-9. doi:10.4137/CIN.S13976
20. Zarrouk Mahjoub S, Mehri S, Ourda F, Finsterer J, Ben AS. Novel m.15434C>a (p.230L>I) mitochondrial Cytb gene missense mutation associated with dilated cardiomyopathy. *ISRN Cardiol*. 2012;2012:251723. doi:10.5402/2012/251723
21. Wang X, Luan Q, Chen Q, Zhao L, Guo Y. Mitochondrial polymorphisms and dysfunction related to aggressive periodontitis: a pilot study. *Oral Diseases*. 2014;20(5):490-498. doi:10.1111/odi.12163
22. Gibson JS, Claassen DO. State-of-the-art pharmacological approaches to reduce chorea in Huntington's disease. *Expert Opinion on Pharmacotherapy*. 2021;22(8):1015-1024. doi:10.1080/14656566.2021.1876666
23. Niemann N, Jankovic J. Treatment of tardive dyskinesia: a general overview with focus on the vesicular monoamine transporter 2 inhibitors. *Drugs*. 2018;78(5):525-541. doi:10.1007/s40265-018-0874-x
24. Furukawa Y, Filiano JJ, Kish SJ. Amantadine for levodopa-induced choreic dyskinesia in compound heterozygotes for GCH1 mutations. *Movement Disorders*. 2004;19(10):1256-1258. doi:10.1002/mds.20194
25. Teixeira AL, Vasconcelos LP, Nunes MDCP, Singer H. Sydenham's chorea: from pathophysiology to therapeutics. *Expert Review of Neurotherapeutics*. 2021;21:913-922. doi:10.1080/14737175.2021.1965883
26. Desai K, Walzade P, Ravat SH, Agarwal PA. Adult-onset isolated Hemichorea revealing iatrogenic hypoparathyroidism and bilateral basal ganglia calcification. *Annals of Indian Academy of Neurology*. 2019;22(4):496-499. doi:10.4103/aian.AIAN_123_18
27. Barnett CP, Mencel JJ, Gecz J, et al. Choreoathetosis, congenital hypothyroidism and neonatal respiratory distress syndrome with intact NKX2-1. *American Journal of Medical Genetics. Part A*. 2012;158A(12):3168-3173. doi:10.1002/ajmg.a.35456
28. Bonomo R, Elia AE, Bonomo G, et al. Deep brain stimulation in Huntington's disease: a literature review. *Neurological Sciences*. 2021;42:4447-4457. doi:10.1007/s10072-021-05527-1
29. Wu Y, Li H, Zhang C, Sun B, Li D, Wu Y. Subthalamic nucleus deep brain stimulation in two siblings with chorea-acanthocytosis. *Neurological Sciences*. 2020;41(6):1623-1625. doi:10.1007/s10072-020-04246-3
30. Aoyagi K, Higuchi Y, Okahara Y, et al. Effects of bilateral pallidal deep brain stimulation on chorea after pulmonary thromboendarterectomy with deep hypothermia and circulatory arrest: a case report. *Acta Neurochirurgica*. 2018;160(2):393-395. doi:10.1007/s00701-017-3433-4

How to cite this article: Finsterer J, Ghosh R. Effective treatment of choreaballism due to an *MT-CYB* variant with haloperidol, tetrabenazine, and antioxidants. *Clin Case Rep*. 2023;11:e7592. doi:10.1002/ccr3.7592