Original Investigation

Clinical, Genetic, and Radiological Features of Extrapyramidal Movement Disorders in Mitochondrial Disease

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IMPORTANCE Extrapyramidal movement disorders associated with mitochondrial disease are difficult to treat and can lead to considerable disability. Moreover, potential new treatment trials on the horizon highlight the importance of genotype-phenotype associations and deep phenotyping of the movement disorders related to mitochondrial disease.

OBJECTIVE To describe the phenotype, genetic etiology, and investigation of extrapyramidal movement disorders in a large and well-defined mitochondrial disease cohort.

DESIGN, SETTING, AND PARTICIPANTS An observational cohort study at a single national referral center. Among 678 patients (87% adults) followed up at the Newcastle mitochondrial disease specialized referral center between January 1, 2000, and January 31, 2015, 42 patients (12 pediatric, 30 adult) with genetic or biochemical evidence of mitochondrial disease and with 1 or more predefined extrapyramidal movement disorders (parkinsonism, dystonia, tremor, chorea, and restless legs syndrome) were included.

MAIN OUTCOMES AND MEASURES We investigated the prevalence and genetic causes of dystonia and parkinsonism as well as radiological findings in the context of movement disorders in mitochondrial disease. All patients were interviewed and examined. All available medical notes and clinical, radiological, and genetic investigations were reviewed.

RESULTS Forty-two patients (mean [SD] age, 37 [25] years; 38% female) with mitochondrial disease (12 pediatric [age range, 4-14 years], 30 adult [age range, 20-81 years]) with extrapyramidal movement disorders were identified. Dystonia manifested in 11 pediatric patients (92%), often in the context of Leigh syndrome; parkinsonism predominated in 13 adult patients (43%), among whom 5 (38%) harbored either dominant (n = 1) or recessive (n = 4) mutations in *POLG*. Eleven adult patients (37%) manifested with either generalized or multifocal dystonia related to mutations in mitochondrial DNA, among which the most common were the m.11778G>A mutation and mutations in *MT-ATP6* (3 of 11 patients [27%] each). Bilateral basal ganglia lesions were the most common finding in brain magnetic resonance imaging, usually associated with generalized dystonia or Leigh syndrome.

CONCLUSIONS AND RELEVANCE Dystonia, often associated with Leigh syndrome, was the most common extrapyramidal movement disorder among pediatric patients with mitochondrial disease. Parkinsonism was the most prevalent extrapyramidal movement disorder in adults and was commonly associated with *POLG* mutations; dystonia was predominantly associated with mitochondrial DNA mutations. These findings may help direct genetic screening in a busy neurology outpatient setting.

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Supplemental content at jamaneurology.com

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JAMA Neurol. 2016;73(6):668-674. doi:10.1001/jamaneurol.2016.0355
Published online April 25, 2016.

Mitochondrial dysfunction is an important cause of neurological disease.[1,2] Mitochondrial disease can present at any age, with extremely varied associated clinical features. Several types of movement disorders have been described in single case reports and small case series of patients with mitochondrial disease.[3] However, the spectrum and characteristics of extrapyramidal movement disorders in the context of a clinically and genetically defined cohort of patients with mitochondrial disease have not been studied in detail. Moreover, in some patients with mitochondrial disease, associated movement disorders such as generalized dystonia are extremely difficult to treat and lead to disability,[4] stressing the need for more detailed understanding and appreciation of these conditions. We interrogated the phenotypic, genetic, and brain imaging findings of extrapyramidal movement disorders in a large, well-defined clinical cohort with mitochondrial disease.

Key Points

Question What extrapyramidal movement disorders are present in patients with mitochondrial disease, and what are their genetic etiologies?

Findings In this cohort study of 42 identified patients with mitochondrial disease (12 pediatric, 30 adult) who had extrapyramidal movement disorders, 11 pediatric patients (92%) had dystonia and 13 adult patients (43%) had parkinsonism, which was commonly associated with mutations in *POLG*.

Meaning These findings may help direct genetic screening in a busy neurology outpatient setting.

Methods

Patients with mitochondrial disease who had movement disorders were identified among 678 (87% adults) of those followed up at the NHS Highly Specialised Service for Mitochondrial Disease in Newcastle, England, between January 1, 2000, and January 31, 2015; most patients had been enrolled to the UK MRC Mitochondrial Disease Patient Cohort Study. All patients were required to have molecular genetic or biochemical evidence of mitochondrial disease.

Among the 2 main movement disorder categories of akinetic-rigid syndromes and hyperkinetic/dyskinetic syndromes, patients with the extrapyramidal movement disorders of parkinsonism (akinetic-rigid) and with dystonia, tremor, chorea, and restless legs syndrome (RLS; hyperkinetic/dyskinetic) were included.[5] Although both myoclonus and ataxia are commonly encountered among patients with mitochondrial disorders,[6,7] these are not conventionally categorized as extrapyramidal disorders and neither were included in this study as primary movement disorders. However, all movement disorder manifestations were noted in the patients included in the study to provide complete phenotypes. All patients were examined and regularly reviewed by 1 or several of us (M.H.M., Y.S.N., G.S.G., A.M.S., P.F.C., D.J.B., R.M., and D.M.T.). All available medical notes as well as clinical, genetic, and brain imaging data were scrutinized.

In this study, affected cases of parkinsonism fulfilled the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for parkinsonian syndrome (ie, bradykinesia with ≥1 of the following: rigidity, 4- to 6-Hz rest tremor, and postural instability).[8] Patients whose condition was compatible with drug-induced parkinsonism or other iatrogenic movement disorders were excluded. Patients with dystonia, tremor, chorea, and RLS were identified based on the respective diagnoses in their medical notes. Likewise, in patients under regular clinical review, diagnoses were further confirmed according to relevant clinical criteria.[9-12] We also scrutinized the therapeutic strategies, including pharmacological, that were used to ameliorate the movement disorder symptoms as well as the clinical responses to these treatments.

This study was approved by the NHS Research Ethics Service North East-Newcastle and North Tyneside 2 Research Ethics Committee and performed under the ethical guidelines issued by our institution for clinical studies, with written informed consent obtained from all participants. High standard of ethics according to the Declaration of Helsinki was applied in all investigations and clinical work described herein.

Results

We identified a total of 42 patients (mean [SD] age, 37 [25] years; 38% female), including 12 pediatric patients (age range, 4-14 years) and 30 adult patients (age range, 20-81 years), from 39 pedigrees with clinically and genetically or biochemically defined mitochondrial disease presenting with 1 or a combination of the predefined movement disorders. The general characteristics of the pediatric patients are summarized in the **Table**, and those of the adult patients are summarized in the eTable in the Supplement. The age at onset refers to the onset of the principal extrapyramidal movement disorder. Owing to limitations in available data, we could not reliably determine the age at onset of the movement disorder in 5 patients (adult patients P18, P21, P30, P35, and P42).

Movement Disorders in Pediatric Patients

Among the 12 pediatric patients (Table), the most common pathogenic mutations were the m.9176T>C mutation in the mitochondrial *MT-ATP6* gene (3 patients [25%]) and mutations in the nuclear *SUCLA2* and *NDUFAF6* genes (2 patients [17%] each). The most common clinical movement disorder in the pediatric patients was dystonia (11 patients [92%]). Four pediatric patients (P2, P4, P6, and P7) presented with chorea or a mixed choreic-dystonic movement disorder. Nine of 12 pediatric patients (75%) had a phenotype compatible with Leigh syndrome (LS).

Movement Disorders in Adult Patients

Among the 30 adult patients (eTable in the Supplement), the most common among the 15 different genetic causes were mutations in *POLG* (7 patients [23%]), followed by the mitochondrial m.11778G>A mutation in *MT-ND4* (3 patients [10%]) and multiple mitochondrial DNA (mtDNA) deletions without an identified nuclear genetic defect (2 patients [7%]). Twelve of

Table. General Characteristics of 12 Pediatric Patients With Mitochondrial Disease and Movement Disorders

Patient No./Sex	Age at Onset/Latest Follow-up, y	Diagnosis	Movement Disorder	Brain MRI Findings	Clinical Course	Other
P1/F	3.5/14	*MT-ND1* mutation m.3688G>A, 84% heteroplasmic in muscle	Generalized dystonia, mostly limbs	Bilateral changes in globus pallidus at age 4 y	Slowly progressive	LS, epilepsy; complex I deficiency; CSF lactate level elevated (24.3 mg/dL)
P2/F	1/13	*MT-ATP6* mutation m.9176T>C	Generalized dystonia, mostly limbs; chorea	ND	Stepwise progression	LS; PEG; sister of patient P3
P3/M	1/14	*MT-ATP6* mutation m.9176T>C	Generalized dystonia, mostly limbs	ND	Stepwise progression	LS; PEG; brother of patient P2
P4/M	1/8	*MT-ATP6* mutation m.9176T>C, 98% heteroplasmic in muscle	Generalized dystonia, mostly limbs; chorea	Increased T2 bilateral changes in putamen and globus pallidus and in dorsal brainstem at age 1 y	Acute onset, stepwise progression	LS; CSF lactate level elevated (33.5 mg/dL); PEG
P5/M	1/10	*MT-ND4* homoplasmic mutation m.11778G>A	Generalized dystonia, trunk and limbs	Hypodevelopment of cerebellar vermis, large cisterna magna at age 1 y	Slowly progressive	LD; visual impairment; PEG
P6/M	1/5	Homozygous *SUCLA2* mutation c.1219C>T (p.Arg407Trp)	Chorea, generalized hypotonia	Increased T2 bilateral changes in putamen and caudate nucleus at age 1.5 y	Slowly progressive	LS; SNHL; PEG
P7/M	1/6	Homozygous *SUCLA2* mutation c.1271delG; p.Gly424Aspfs*18	Choreic-dystonic movement disorder, limbs	Increased T2 speckled appearance in bilateral basal ganglia changes at age 1 y	Slowly progressive	LS; SNHL; PEO; PEG
P8/M	1/7	Compound heterozygous *FARS2* mutations: c.973G>T (p.Asp325Tyr) and an 88-kb (6p25.1) deletion	Generalized dystonia, mostly limbs	Increased T2 bilateral subcortical changes, thinning of corpus callosum	Slowly progressive	LD, severe epilepsy; previously published[13]
P9/M	1/4	Homozygous *NDUFAF6* mutation c.226T>C (p.Ser76Pro)	Generalized dystonia, all limbs; levodopa useful	Increased T2 bilateral changes in putamen, parietal cerebral white matter, dorsal pons at age 2 y	Stepwise progression	LS; complex I deficiency; PEG; brother of patient P10
P10/M	1/12	Homozygous *NDUFAF6* mutation c.226T>C (p.Ser76Pro)	Generalized dystonia, all limbs; levodopa alleviated dystonia but increased aggression	Increased T2 bilateral changes in caudate and putamen nucleus at age 3 y	Stepwise progression	LS; complex I deficiency; PEG; brother of patient P9
P11/F	1/5	Homozygous *PDHX* mutation c.1158C>T (p.Gln387*)	Dystonic spasms, limbs	Generalized atrophy, atrophic corpus callosum, atrophic periventricular white matter	Slowly progressive	LD, severe epilepsy; SNHL
P12/M	1/5	Homozygous *MTFMT* mutation c.626C>T (p.Arg181Serfs*6)	Multifocal dystonia, limbs	Increased T2 bilateral changes in putamen, globus pallidus, subthalamic nucleus, and dorsal brainstem at age 4 y	Stepwise progression	LS; complex I and IV deficiency; elevated CSF lactate level (40.5 mg/dL); motor developmental delay, speech delay

Abbreviations: CSF, cerebrospinal fluid; kb, kilobase; LD, learning disability; LS, Leigh syndrome; MRI, magnetic resonance imaging; ND, not done; PEG, percutaneous endoscopic gastrostomy; PEO, progressive external ophthalmoplegia; SNHL, sensorineural hearing loss.

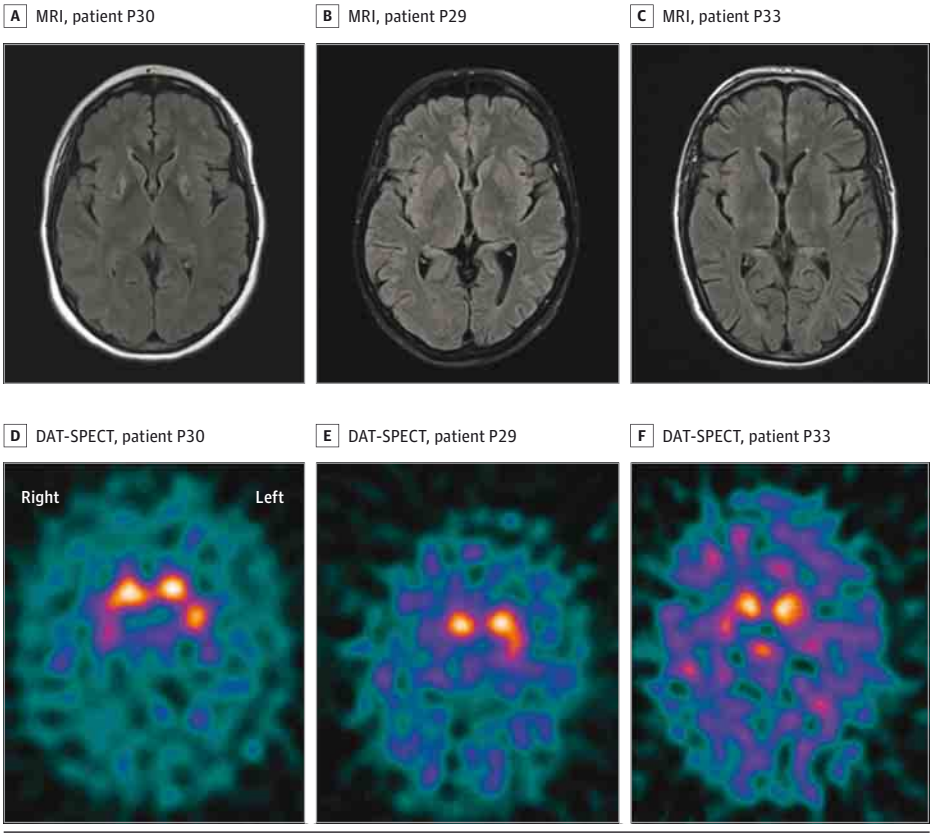
SI conversion factor: To convert CSF lactate level to millimoles per liter, multiply by 0.111.

the 30 adult patients (40%) presented with generalized or multifocal dystonia and 6 (20%) presented with focal dystonia (including 1, patient P19, with vocal cord dystonia). Parkinsonism was present in 13 adult patients (43%), and 5 of these 13 (patients P32, P33, P34, P36, and P37) harbored mutations in *POLG*. Five adult patients had RLS (3 of whom also had parkinsonism): 3 with *POLG* mutations (patients P35-P37), 1 with multiple mtDNA deletions (patient P41; genetic cause undetermined), and 1 with an *SDHA* mutation (patient P39). Chorea or a choreic-dystonic movement disorder was present in 2 adult patients (patients P23 and P26). Action tremor and rapid eye movement sleep behavioral disorder were present in 1 patient each (patients P30 and P41, respectively). Seven of the 30 adult patients (23%) had a phenotype compatible with LS.

Patients With Dystonia and LS

In the combined group of pediatric and adult patients, the single most common cause of generalized dystonia was the mitochondrial m.11778G>A mutation (n = 4). Overall, a pathogenic mtDNA mutation was detected in 14 of the 18 pediatric and adult patients (78%) with generalized dystonia. Among pediatric patients with a phenotype compatible with LS, the mean (SD) age at disease onset was 1.3 (0.8) years (median, 1 year; interquartile range [IQR], 0 years; range, 1-3.5 years), whereas the mean (SD) age at latest follow-up was 9.0 (4.2) years (median, 8 years; IQR, 8 years; range, 4-14 years). Among the adult patients with LS, the mean (SD) age at disease onset was 2.1 (1.4) years (median, 1.75 years; IQR, 2 years; range, 1-4 years), whereas the mean (SD) age at latest follow-up was 29 (7.0) years (median, 28 years; IQR, 5 years; range, 21-40 years). Generalized dystonia manifested early in life with a mean (SD) age at onset of 2.7 (4.9) years (median, 1 year; IQR, 1 year; range, 1-20 years), whereas parkinsonism presented at later age with mean (SD) age at onset of 42 (16) years (median, 50 years; IQR, 29 years; range, 18-55 years).

Figure. Brain Magnetic Resonance Imaging (MRI) and Dopamine Transporter Single-Photon Emission Computed Tomography (DAT-SPECT) Imaging Findings in Patients With Mitochondrial Disease



A and D, Bilateral putaminal lesions in brain MRI (A) and bilaterally reduced striatal uptake in DAT-SPECT imaging (D) in patient P30. B and E, Normal brain MRI findings (B) but bilaterally reduced striatal uptake in DAT-SPECT imaging (E) in patient P29. C and F, Cerebral and cerebellar atrophy but normal basal ganglia in brain MRI (C) and bilaterally reduced striatal uptake in DAT-SPECT imaging (F) in patient P33.

Brain Imaging

Structural brain imaging data were available for 35 patients. Brain magnetic resonance imaging most often revealed T2-weighted and fluid-attenuated inversion recovery hyperintensities in basal ganglia (mostly in putamen and globus pallidus), bilaterally in 16 patients and unilaterally in only 1 patient (patient P18). Brain computed tomographic scans were available in 7 patients; basal ganglia calcification was not evident. Cerebellar atrophy was present in 6 patients (patients P11, P19, P20, P33, P34, and P42). Three patients (patients P29, P32, and P35) had normal brain imaging findings. Dopamine transporter single-photon emission computed tomography (DAT-SPECT) data, in our institute using the iodine 123 ([^{123}I])-labeled FP-CIT (N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-[^{123}I]iodophenyl) nortropane) radioligand, were available for 12 adult patients, 9 of whom had abnormal findings suggestive of a presynaptic nigrostriatal dopaminergic defect. Interestingly, the 3 patients with normal DAT-SPECT findings presented clinically with parkinsonism (patient P38), RLS (patient P41), or a combination of the two (patient P39). Among the 9 patients with abnormal DAT-SPECT findings (**Figure**), 7 presented with parkinsonism as the predominant movement disorder. One patient with abnormal DAT-SPECT findings presented with RLS and another presented with unspecified tremor (patients P35 and P30, respectively). Among the 9 patients with abnormal DAT-SPECT findings, 6 harbored *POLG* mutations (patient P36 with a dominant mutation and patients P32-P35 and P37 with recessive mutations), whereas the remaining 3 patients all had different genetic diagnoses (patient P29 with a single large-scale mtDNA deletion, patient P30 with compound heterozygous *MTFMT* mutations, and patient P40 with a dominant *SDHA* mutation). No brain imaging data were available in 2 pediatric patients (patients P2 and P3) and 3 adult patients (patients P21, P28, and P31).

Medications to Treat Movement Disorders

Data for medications used specifically to treat movement disorders were available in 14 patients: 2 pediatric patients (patients P9 and P10) and 12 adult patients. Levodopa was used in 12 patients: 6 patients (all adults) with parkinsonism as the predominant movement disorder and 6 patients (2 pediatric and 4 adult patients) who mainly presented with dystonia. Among the 6 adult patients with parkinsonism who received levodopa, 3 responded well but the other 3 did not. Both pediatric patients treated for generalized dystonia responded well to levodopa, whereas among the 4 levodopa-treated adult patients with dystonia, only 1 responded well.

Five patients (patients P13 and P24-P27) with dystonia were treated with oral baclofen and 6 patients (patients P13, P19, P20, and P24-P26) with dystonia received botulinum neurotoxin injections. Four of the 5 patients who received oral baclofen for

dystonia tolerated it well, although they lacked noticeable clinical improvement (patients P13, P24, P25, and P27). Botulinum neurotoxin was generally well tolerated and effective in the treatment of focal or multifocal dystonia. Six patients (patients P13, P20, and P24-P27) had received at least 2 different treatments targeting dystonia. Poor tolerance of oral baclofen, tizanidine hydrochloride, trihexyphenidyl hydrochloride, or amantadine hydrochloride was noted in 3 patients (patients P26, P27, and P34). None of the patients received intrathecal baclofen or deep brain stimulation, although deep brain stimulation was considered but not deemed suitable for 2 patients (patients P24 and P25). No pediatric patients received medications other than levodopa.

Discussion

In our study of a large and clinically well-defined cohort of patients with mitochondrial disease (predominantly adults [87%]) including patients from all over the United Kingdom, we identified 12 pediatric and 30 adult patients who presented with the extrapyramidal features of parkinsonism, dystonia, tremor, chorea, or RLS. Among the pediatric patients, dystonia, most commonly as part of LS, was the predominant extrapyramidal movement disorder. Among the adult patients, parkinsonism was the predominant extrapyramidal movement disorder, followed by generalized or multifocal dystonia, with the other predefined movement disorder presentations being far less common.

Parkinsonism is a well-recognized albeit uncommon presentation associated with pathogenic mutations in *POLG*. Among the 5 patients with parkinsonism and *POLG* mutations in our cohort, 1 patient (patient P36) harbored a dominant mutation that has previously been reported.[14] Interestingly, the other 4 patients harbored either homozygous (patient P32) or compound heterozygous (patients P33, P34, and P37) mutations in the linker region of *POLG*, suggesting that parkinsonism is also part of the clinical spectrum of recessive mutations in *POLG*. Mitochondrial parkinsonism has previously been reported also in the context of various mtDNA mutations, including the m.8344A>G mutation[15] and large-scale "common" mtDNA deletions.[16] In our cohort, 2 patients with *SDHA* mutations (patients P39 and P40) and 1 with *RRM2B*-related mitochondrial disease (patient P38) presented with parkinsonism as part of their phenotype. Parkinsonism has recently been reported in association with pathogenic mutations in *OPA1*.[17] However, among our small cohort of 22 patients with *OPA1* mutations, we have not observed parkinsonism or other extrapyramidal movement disorders. Clinical distinction between idiopathic Parkinson disease (IPD) overlapping a mitochondrial disorder and a true mitochondrial parkinsonism is not always straightforward. Parkinsonism related to *POLG* mutations is the best characterized type of parkinsonism associated with mitochondrial disease, and it can closely mimic IPD given the typically asymmetric clinical symptoms at onset, good response to levodopa, and imaging evidence of nigrostriatal dysfunction.[14] However, our present data suggest that mitochondrial parkinsonism usually has earlier age at onset than IPD and that asymmetric DAT-SPECT findings make a good response to levodopa more likely (patients P29 and P36 vs P32 and P40; eTable in the Supplement).

In the context of mitochondrial disease, dystonia has been mostly reported in association with LS and Leber hereditary optic neuropathy mutations, but it has also been reported with several other mtDNA mutations.[4,18,19] Two patients in this study (patients P31 and P32) harbored recessive *POLG* mutations and presented with dystonia as part of their phenotype. Although previously reported,[20] we suggest that dystonia may have been overlooked owing to prominence of other clinical features of *POLG*-related disease. Interestingly, we found 6 patients (patients P2-P4 and P20-P22) with *MT-ATP6* mutations presenting with dystonia, although 2 of these (patients P2 and P3) were from the same pedigree and 5 of these occurred in the context of LS. One patient with the m.8344A>G mutation presented with vocal cord dystonia as part of the phenotype (patient P19); to our knowledge, this association has previously been reported in only 1 other patient.[21] The m.3688G>A mutation (patient P1) was reported earlier in a child with LS,[22] and the m.13513G>A mutation (patient P27) is a recognized cause of LS.[23] Among the other genetic defects associated with dystonia in this study (mostly in the context of a complex phenotype such as LS), *FARS2* mutations are a recognized cause of LS or early-onset encephalopathy syndrome.[24] The phenotype of the patient with a *PDHX* mutation (patient P11) is similar to the previously reported case.[25] Mutations in *SUCLA2* (patients P6 and P7) and *NDUFAF6* (*C8orf38*) (patients P9 and P10) have also been reported to result in LS-like phenotypes.[26,27]

The 2 patients in our study with *MTFMT* mutations (patients P12 and P30) presented with LS. A common presentation associated with pathogenic *MTFMT* mutations is LS with ataxia, hypotonia, and psychomotor retardation.[28] Chorea and RLS have both been only rarely reported in association with mitochondrial disease.[29,30] We found 6 patients presenting with chorea or a mixed choreic-dystonic movement disorder and 5 patients presenting with RLS. However, both were typically part of a more complex phenotype. Monoamine neurotransmitter disorders often present with parkinsonism or generalized dystonia, and secondary cerebrospinal fluid neurotransmitter abnormalities have been reported in mitochondrial disorders.[31] Unfortunately, no cerebrospinal fluid neurotransmitter data were available for any of the patients described in this study.

The use of FP-CIT-SPECT is an established method for in vivo assessment of presynaptic dopaminergic function.[32] However, there are only a few studies reporting the findings in DAT imaging in patients with mitochondrial disease along with parkinsonism or other movement disorders. A bilateral nigrostriatal dopaminergic defect has been reported both in patients with *POLG*-related parkinsonism[14,33] and in patients with *POLG*-related mitochondrial disease without clinical parkinsonism.[34] Among the 12 patients with DAT-SPECT data in our study, a reduction in presynaptic DAT binding was observed in 9 patients. Among these, parkinsonism was the dominant movement disorder in 7; the main movement disorder was action tremor in 1 patient (patient P30) and RLS in

another (patient P35). Six of these 9 patients with abnormal DAT-SPECT imaging findings harbored *POLG* mutations. Interestingly, and in line with the previous study by Tzoulis et al,[34] DAT-SPECT findings were abnormal in all patients with *POLG* mutations who had available imaging data. Among the 3 patients with normal DAT-SPECT findings, 1 harbored a mutation of *RRM2B* (patient P38) and another had mutations in *SDHA*,[35] resulting in mitochondrial complex II deficiency (patient P39). In the third patient, multiple mtDNA deletions in muscle were detected but no underlying gene defect was revealed (patient P41).

Among patients with parkinsonism and dystonia, there were several reasons some patients did not receive levodopa at any time, including early onset of disease and heavier overall disease burden. In the case of some pediatric patients, the parents may have been reluctant toward medical treatments. Levodopa treatment and responses to levodopa are noted in the Table and in the eTable in the Supplement for all patients who received this medication. Among the 12 patients who used levodopa, the predominant movement disorder was dystonia in 6 patients and parkinsonism in the other 6. The fact that we do not know exactly how the pathophysiology of mitochondrial parkinsonism differs from IPD and indeed whether there are several mechanisms leading to similar phenotypes renders rational pharmacotherapy more challenging; at present, it seems that the possible benefit of levodopa in mitochondrial movement disorders should be determined case by case, although asymmetric DAT-SPECT findings probably indicate a higher likelihood of a good response to levodopa in patients with parkinsonism.

Therapeutic trials are warranted to establish the symptomatic efficacy of levodopa in patients with generalized dystonia or parkinsonism associated with mitochondrial disease. Patients with focal or multifocal dystonia benefited from botulinum neurotoxin injections. Although oral baclofen was well tolerated in most patients with generalized dystonia, the clinical responses were modest. There is at present little evidence to guide decisions on the medical treatment of mitochondrial movement disorders, and we acknowledge that data on pharmacological therapies targeting movement disorders were not extensive in this study. However, as movement disorders such as generalized dystonia can result in long-term disability in patients with mitochondrial disease, active pursuit of symptomatic relief and improvement of quality of life are warranted.

Conclusions

This study on the extrapyramidal movement disorders of parkinsonism, dystonia, RLS, tremor, and chorea in a large cohort of patients with mitochondrial disease suggests that dystonia, often in the context of LS, is the most common movement disorder among pediatric patients. Among adult patients, parkinsonism is the most common movement disorder, followed by generalized or multifocal dystonia. Mitochondrial parkinsonism was commonly associated with *POLG* mutations, whereas mitochondrial dystonia would appear to be predominantly associated with mtDNA mutations, commonly the m.11778G>A mutation or mutations in *MT-ATP6*. As many patients with mitochondrial movement disorders, even those with severe disability associated with LS, live well into adulthood, we suggest that clinical trials are needed to improve the treatment of these patients. Research-based evidence on the treatment of mitochondrial movement disorders remains very limited. However, patients with generalized dystonia and with parkinsonism may benefit from levodopa, and therapeutic trials with this medication are warranted.

ARTICLE INFORMATION

Accepted for Publication: February 2, 2016.

Published Online: April 25, 2016. doi:10.1001/jamaneurol.2016.0355.

Author Contributions: Dr Martikainen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Martikainen, Ng, Gorman, Burn, McFarland, Turnbull.
Acquisition, analysis, or interpretation of data: Martikainen, Ng, Gorman, Alston, Blakely, Schaefer, Chinnery, Taylor, McFarland, Turnbull.
Drafting of the manuscript: Martikainen.
Critical revision of the manuscript for important intellectual content: All authors.
Obtained funding: Turnbull.
Administrative, technical, or material support: Ng, Alston, Turnbull.
Study supervision: Gorman, Schaefer, Chinnery, McFarland, Turnbull.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by the Wellcome Trust. Dr Martikainen is supported by the Sigrid Jusélius Foundation. Dr Ng is supported by the Medical Research Council (MRC) Centre for Neuromuscular Diseases. Drs Gorman and Burn are supported by the National Institute for Health Research. Ms Alston is supported by doctoral fellowship NIHR-HCS-D12-03-04 from the National Institute for Health Research. Drs Chinnery and Taylor are supported by grant G0601943 from the MRC Centre for Translational Muscle Disease Research. Drs Chinnery, Taylor, and McFarland are supported by grant 096919Z/11/Z from the Wellcome Trust Centre for Mitochondrial Research. Dr Chinnery is a Wellcome Trust Senior Fellow in Clinical Science (grant 101876/Z/13/Z) and National Institute for Health Research Senior Investigator and is supported by grant MC_UP_1501/2 from the MRC Mitochondrial Biology Unit. Dr Burn is supported by Parkinson's UK, the Michael J. Fox Foundation, and the Wellcome Trust. Drs Taylor, McFarland, and Turnbull are supported by the National Health Service Highly Specialised Commissioners, which fund the "Rare Mitochondrial Disorders of Adults and Children" Diagnostic Service in Newcastle upon Tyne. Dr McFarland is supported by the MRC. Dr Turnbull is supported by grant G906919 from the Wellcome Trust Centre for Mitochondrial Research, by Newcastle University Centre for Ageing and Vitality (supported by the Biotechnology and Biological Sciences Research Council and grant G016354/1 from the MRC), grant G000608-1 from the MRC Centre for Neuromuscular Diseases, grant G0800674 from the MRC Centre for Translational Research in Neuromuscular Disease Mitochondrial Disease Patient Cohort, the Lily Foundation, and the National Institute for Health Research Biomedical Research Centre in Age and Age Related Diseases award to the Newcastle upon Tyne Hospitals NHS Foundation Trust

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Previous Presentation: This paper was presented at the 68th Annual Meeting of the American Academy of Neurology; April 16, 2016; Vancouver, British Columbia, Canada.

REFERENCES

1. McFarland R, Taylor RW, Turnbull DM. A neurological perspective on mitochondrial disease. *Lancet Neurol*. 2010;9(8):829-840.

2. Gorman GS, Schaefer AM, Ng Y, et al. Prevalence of nuclear and mitochondrial DNA mutations

related to adult mitochondrial disease. *Ann Neurol*. 2015;77(5):753-759.

3. Moustris A, Edwards MJ, Bhatia KP. Movement disorders and mitochondrial disease. *Handb Clin Neurol*. 2011;100:173-192.

4. McFarland R, Chinnery PF, Blakely EL, et al. Homoplasmy, heteroplasmy, and mitochondrial dystonia. *Neurology*. 2007;69(9):911-916.

5. Abdo WF, van de Warrenburg BP, Burn DJ, Quinn NP, Bloem BR. The clinical approach to movement disorders. *Nat Rev Neurol*. 2010;6(1):29-37.

6. Mancuso M, Orsucci D, Angelini C, et al. Myoclonus in mitochondrial disorders. *Mov Disord*. 2014;29(6):722-728.

7. Lax NZ, Hepplewhite PD, Reeve AK, et al. Cerebellar ataxia in patients with mitochondrial DNA disease: a molecular clinicopathological study. *J Neuropathol Exp Neurol*. 2012;71(2):148-161.

8. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*. 1992;55(3):181-184.

9. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord*. 2013;28(7):863-873.

10. Deuschl G, Bain P, Brin M; Ad Hoc Scientific Committee. Consensus statement of the Movement Disorder Society on tremor. *Mov Disord*. 1998;13(suppl 3):2-23.

11. Sanger TD, Chen D, Fehlings DL, et al. Definition and classification of hyperkinetic movements in childhood. *Mov Disord*. 2010;25(11):1538-1549.

12. Benes H, Walters AS, Allen RP, Hening WA, Kohnen R. Definition of restless legs syndrome, how to diagnose it, and how to differentiate it from RLS mimics. *Mov Disord*. 2007;22(suppl 18):S401-S408.

13. Almalki A, Alston CL, Parker A, et al. Mutation of the human mitochondrial phenylalanine-tRNA synthetase causes infantile-onset epilepsy and cytochrome *c* oxidase deficiency. *Biochim Biophys Acta*. 2014;1842(1):56-64.

14. Luoma P, Melberg A, Rinne JO, et al. Parkinsonism, premature menopause, and mitochondrial DNA polymerase gamma mutations: clinical and molecular genetic study. *Lancet*. 2004;364(9437):875-882.

15. 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.

16. Zhang J, Montine TJ, Smith MA, et al. The mitochondrial common deletion in Parkinson's disease and related movement disorders. *Parkinsonism Relat Disord*. 2002;8(3):165-170.

17. Carelli V, Musumeci O, Caporali L, et al. Syndromic parkinsonism and dementia associated with *OPA1* missense mutations. *Ann Neurol*. 2015;78(1):21-38.

18. Rahman S, Blok RB, Dahl HH, et al. Leigh syndrome: clinical features and biochemical and DNA abnormalities. *Ann Neurol*. 1996;39(3):343-351.

19. Sudarsky L, Plotkin GM, Logigian EL, Johns DR. Dystonia as a presenting feature of the 3243 mitochondrial DNA mutation. *Mov Disord*. 1999;14(3):488-491.

20. Hinnell C, Haider S, Delamont S, Clough C, Hadzic N, Samuel M. Dystonia in mitochondrial spinocerebellar ataxia and epilepsy syndrome associated with novel recessive *POLG* mutations. *Mov Disord*. 2012;27(1):162-163.

21. Peng Y, Crumley R, Ringman JM. Spasmodic dysphonia in a patient with the A to G transition at nucleotide 8344 in mitochondrial DNA. *Mov Disord*. 2003;18(6):716-718.

22. Valente L, Piga D, Lamantea E, et al. Identification of novel mutations in five patients with mitochondrial encephalomyopathy. *Biochim Biophys Acta*. 2009;1787(5):491-501.

23. Shanske S, Coku J, Lu J, et al. The G13513A mutation in the *ND5* gene of mitochondrial DNA as a common cause of MELAS or Leigh syndrome: evidence from 12 cases. *Arch Neurol*. 2008;65(3):368-372.

24. Elo JM, Yadavalli SS, Euro L, et al. Mitochondrial phenylalanyl-tRNA synthetase mutations underlie fatal infantile Alpers encephalopathy. *Hum Mol Genet*. 2012;21(20):4521-4529.

25. Schiff M, Miné M, Brivet M, et al. Leigh's disease due to a new mutation in the *PDHX* gene. *Ann Neurol*. 2006;59(4):709-714.

26. Ostergaard E, Hansen FJ, Sorensen N, et al. Mitochondrial encephalomyopathy with elevated methylmalonic acid is caused by *SUCLA2* mutations. *Brain*. 2007;130(pt 3):853-861.

27. Pagliarini DJ, Calvo SE, Chang B, et al. A mitochondrial protein compendium elucidates complex I disease biology. *Cell*. 2008;134(1):112-123.

28. Haack TB, Gorza M, Danhauser K, et al. Phenotypic spectrum of eleven patients and five novel *MTFMT* mutations identified by exome sequencing and candidate gene screening. *Mol Genet Metab*. 2014;111(3):342-352.

29. Morimoto N, Nagano I, Deguchi K, et al. Leber hereditary optic neuropathy with chorea and dementia resembling Huntington disease. *Neurology*. 2004;63(12):2451-2452.

30. Aitken H, Gorman G, McFarland R, Roberts M, Taylor RW, Turnbull DM. Clinical reasoning: blurred vision and dancing feet: restless legs syndrome presenting in mitochondrial disease. *Neurology*. 2009;72(18):e86-e90.

31. Ng J, Papandreou A, Heales SJ, Kurian MA. Monoamine neurotransmitter disorders: clinical advances and future perspectives. *Nat Rev Neurol*. 2015;11(10):567-584.

32. Ba F, Martin WR. Dopamine transporter imaging as a diagnostic tool for parkinsonism and related disorders in clinical practice. *Parkinsonism Relat Disord*. 2015;21(2):87-94.

33. Bandettini di Poggio M, Nesti C, Bruno C, Meschini MC, Schenone A, Santorelli FM. Dopamine-agonist responsive Parkinsonism in a patient with the SANDO syndrome caused by *POLG* mutation. *BMC Med Genet*. 2013;14:105.

34. Tzoulis C, Tran GT, Schwarzlmüller T, et al. Severe nigrostriatal degeneration without clinical parkinsonism in patients with polymerase gamma mutations. *Brain*. 2013;136(pt 8):2393-2404.

35. Birch-Machin MA, Taylor RW, Cochran B, Ackrell BA, Turnbull DM. Late-onset optic atrophy, ataxia, and myopathy associated with a mutation of a complex II gene. *Ann Neurol*. 2000;48(3):330-335.