

# Leigh syndrome followed by parkinsonism in an adult with homozygous c.626C>T mutation in *MTFMT*

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## Abstract

### Objective

To report the clinical, radiologic, biochemical, and molecular characteristics in a 46-year-old participant with adult-onset Leigh syndrome (LS), followed by parkinsonism.

### Methods

Case description with diagnostic workup included blood and CSF analysis, skeletal muscle investigations, blue native polyacrylamide gel electrophoresis, whole exome sequencing targeting nuclear genes involved in mitochondrial transcription and translation, cerebral MRI, 123I-FP-CIT brain single-photon emission computed tomography (SPECT), and C-11 raclopride positron emission tomography (PET).

### Results

The participant was found to have a defect in the oxidative phosphorylation caused by a c.626C>T mutation in the gene coding for mitochondrial methionyl-tRNA formyltransferase (*MTFMT*), which is a pathogenic mutation affecting intramitochondrial protein translation. The proband had a normal concentration of lactate in blood and no abnormal microscopic findings in skeletal muscle. Cerebral MRI showed bilateral lesions in the striatum, mesencephalon, pons, and medial thalamus. Lactate concentration in CSF was increased. FP-CIT SPECT and C-11 raclopride PET demonstrated a defect in the dopaminergic system.

### Conclusions

We report on a case with adult-onset LS related to a *MTFMT* mutation. Two years after the onset of symptoms of LS, the proband developed a parkinson-like disease. The c.626C>T mutation is the most common pathogenic mutation found in 22 patients reported earlier in the literature with a defect in *MTFMT*. The age of the previously reported cases varied between 14 months and 24 years. Our report expands the phenotypical spectrum of *MTFMT*-related neurologic disease and provides clinical evidence for involvement of *MTFMT* in extrapyramidal syndromes.

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## Glossary

**bMRI** = brain magnetic resonance imaging; **BN-PAGE** = blue native polyacrylamide gel electrophoresis; **EPS** = extrapyramidal symptom; **FLAIR** = fluid attenuated inversion recovery; **FP-CIT** = N-(3-fluoropropyl)-2beta-carbomethoxy-3beta-(4-iodophenyl)nortropine; **LS** = Leigh syndrome; **OXPHOS** = oxidative phosphorylation; **PD** = Parkinson disease; **PET** = positron emission tomography; **SPECT** = single-photon emission computed tomography; **WES** = whole exome sequencing.

Leigh syndrome (LS) is a devastating neurometabolic disorder occurring mainly in infants and young children. Affected children initially develop normally but present between the age of 2 and 9 months with signs of motor regression, weakness, hypotonia, weak cry, and failure to thrive. Shortly thereafter, signs of brainstem dysfunction are seen, including respiratory pattern abnormalities, nystagmus, ptosis, and ophthalmoparesis. Other neurologic manifestations include pyramidal tract signs, ataxia, dystonia, tremor, and seizures, eventually progressing to death, usually within 2 years after onset of symptoms. Pathologic hallmarks of the disease are bilaterally symmetrical foci characterized by spongiform necrosis with capillary proliferation in the midbrain and striatum.<sup>1,2</sup> The incidence is 1 in 40,000.<sup>3</sup> Rarely, the onset of symptoms is in late childhood, adolescence, or adulthood.

Gene defects associated with LS are located in mitochondrial or nuclear genes involved in the biosynthesis of oxidative phosphorylation (OXPHOS) complexes I, II, III, IV, and V, or involved in the biosynthesis of coenzyme Q or pyruvate dehydrogenase complex. Mutations in the gene coding for mitochondrial methionyl-tRNA formyltransferase (*MTFMT*) were reported earlier as the cause of LS.<sup>4-6</sup>

In this study, we describe a patient with adult-onset LS caused by a homozygous pathogenic mutation in *MTFMT*. Our observation broadens the clinical spectrum of *MTFMT*-related disease.

## Methods

Case description with a diagnostic workup included results from blood and CSF analysis, skeletal muscle investigations, blue native polyacrylamide gel electrophoresis (BN-PAGE), whole exome sequencing (WES) targeting nuclear genes involved in mitochondrial transcription and translation, brain MRI (bMRI), 123I-FP-CIT brain single-photon emission computed tomography (SPECT), and C-11 raclopride positron emission tomography (PET). Written informed consent for research was obtained from the participant and her guardian.

### Data availability

Anonymized data will be shared by request from any qualified investigator.

## Case description

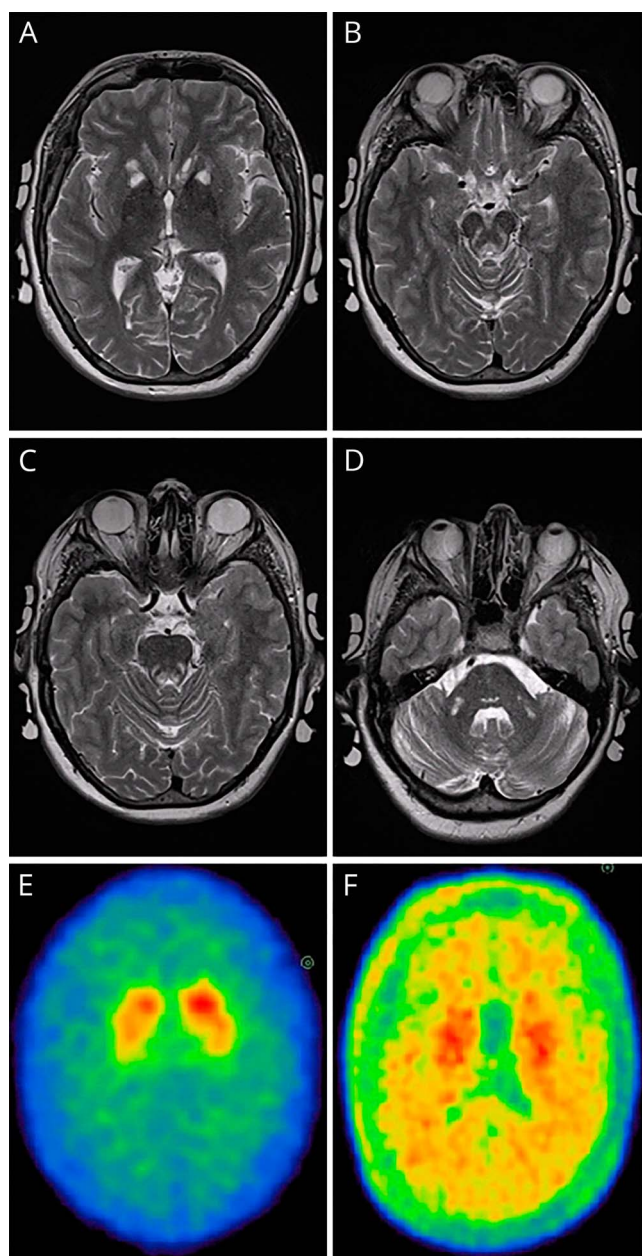
### Clinical history

A 44-year-old woman was admitted to the department of neurology after 1 week of dizziness, vomiting, somnolence,

and subfebrility (37.8°C). Before admission, she had complained of double vision. Divergent eye motility was observed intermittently. Her medical history revealed mild cognitive impairment, early-onset bilateral sensorineural hearing loss, autism spectrum disorder, obsessive-compulsive behavior, depression, osteoporosis, obesity, and mild chronic obstructive pulmonary disease. Vitamin B12 hypovitaminosis was diagnosed in the past as the cause of pernicious anemia. Neurologic examination on admission to the hospital was limited because of poor cooperation and somnolence. Slight nuchal rigidity, gait ataxia, hyperreflexia, plantar reflexes in extension, and absence of sensorimotor dysfunction were noticed. Neuroophthalmologic examination showed upward gaze palsy, downward gaze paresis, bilateral miosis not reacting to light and preserved convergence, and ability to abduct the eyes. Coordination could not be tested because of insufficient cooperation. Urinary retention was detected on arrival. In the 3 weeks after admission, a deterioration of gait and balance was seen, as well as lack of initiative. Slight speech difficulties (hypophonia and tachylalia) were detected, as well as slow movements. Differential diagnosis included Wernicke encephalopathy, acute demyelinating disease, and LS. Acute stroke was excluded with acute brain CT. IV vitamin B-complex, including thiamin, was started but did not change symptoms within the first days. Later on, her clinical condition stabilized. Gait, balance, and speech recovered slowly over a period of 1 month, although a high-pitched tachylalia remained present and appeared to be already known before admission. Gradual improvement of diplopia and bladder dysfunction was seen, although the sensorineural hearing loss was worsening.

### Technical investigations

bMRI showed nonacute lacunar or cystic T2-hyperintense lesions in the basal ganglia (caudate nucleus and putamen) and remarkable acute symmetrical fluid attenuated inversion recovery (FLAIR)-/T2-hyperintense lesions in the mesencephalon, suggestive of Leigh disease (figure, A and B). Follow-up bMRI 1 month later showed that brainstem lesions were more pronounced in the mesencephalon and pons, extending into the medial thalamus bilaterally. bMRI 3 months after symptom onset showed tissue loss and gliosis, with reduced FLAIR hyperintense signals in the mesencephalic area, in both thalami and new lesions in the middle cerebellar peduncles (figure, C and D). CSF analysis on the first admission was normal, except for increased lactate concentration (38 mg/dL, normal 10–22), confirmed a few days later (33 mg/dL). Serum lactate, vitamin B12, and thiamin were normal. Ophthalmologic examination showed abnormal eye motility but no signs of optic atrophy or of retinitis pigmentosa. Ultrasound examination of the heart revealed mild



Brain MRI on admission showing T2 nonacute neostriatal cystic lesions (A), hyperintense lesions in mesencephalon and pons (B and C), and subacute lesions in middle cerebellar peduncles (D). I-123 FP-CIT SPECT (E) and C-11 raclopride PET (F) showing bilateral reduced presynaptic dopamine transport and bilateral postsynaptic dopaminergic impairment. SPECT = single-photon emission computed tomography.

left ventricular hypertrophy (interventricular septum and left ventricular posterior wall thickness of 13 mm). The urinary bladder was atonic. The clinical presentation and technical and biochemical investigations were suggestive of a mitochondrial disease compatible with LS. A skeletal muscle biopsy (M. quadriceps femoris) and skin biopsy were performed. Histologic analysis of skeletal muscle showed no abnormalities. Ragged red fibers were not detected. Spectrophotometric measurement of the OXPHOS complex activities revealed a combined deficiency of complexes I and IV. In cultured skin fibroblasts, a significantly

decreased activity of complex IV was found (complex I not assessed) (table). BN-PAGE, followed by in-gel activity staining using isolated mitochondria from cultured skin fibroblasts, confirmed decreased activity of complexes I and IV, and in addition, showed the presence of complex V subcomplexes. These findings together are the hallmark of defective intramitochondrial protein synthesis. Sequencing of the complete mitochondrial genome with massive parallel sequencing methodology in leukocytes and skeletal muscle did not reveal a pathogenic alteration. DNA sequencing of the *POLG* gene was normal, and comparative genomic hybridization microarray analysis showed no abnormalities. Molecular workup by WES targeting nuclear genes revealed a homozygous missense mutation (c.626C>T, p.Ser209Leu) in *MTFMT* (NM 139242.3). Biotin-thiamin responsive basal ganglia disease caused by a mutation in *SLC19A3* was excluded. Parents were not available for testing.

### Long-term follow-up

Two years after the onset of symptoms of LS, at the age of 46 years, extrapyramidal symptoms (EPS) were seen characterized by marked hypomimia, mild bradykinesia, difficulties with fine motor skills, discrete cogwheel rigidity, diminished arm swing amplitude, disturbed finger movements, slight dysdiadochokinesis, and hypophonia. Tremor was not observed. Gait and balance were near normal. The effect of EPS on daily activities was limited, and, therefore, medical treatment was not started. EPS remained stable over the course of 5 years after the onset. Thereafter, a mild positional tremor of both hands (left > right) was noticed and bradykinesia worsened. Brain I-123 FP-CIT SPECT scan showed bilateral symmetrical reduced FP-CIT binding in the basal ganglia (figure, E). Brain C-11 raclopride PET revealed severe bilateral neostriatal reduction of C-11 raclopride (figure, F). A therapeutic trial with levodopa was started with limited beneficial effect on tremor and bradykinesia.

### Discussion

LS is usually reported as infantile subacute necrotizing encephalomyelopathy, a neurodegenerative disorder clinically characterized by variable neurologic signs. Bilateral lesions in the striatum are typically seen on brain imaging studies. The onset of symptoms in infancy or early childhood is usually triggered by metabolic or infectious stress, followed by rapid neurologic deterioration, often leading to death.<sup>7</sup> Long-term survival after early-onset LS and atypical late-onset variants has been reported.<sup>8</sup> The number of patients with late-childhood-, adolescent-, or adult-onset LS is limited, and only in a few, the genetic defect was identified. The *MTFMT* gene product is essential for efficient mitochondrial translation initiation and function. The protein is involved in formylation of a portion of the Met-tRNA<sup>Met</sup> pool to generate formylmethionyl-tRNA needed for initiation of protein synthesis in mitochondria.<sup>4,9</sup> We report here the oldest patient so far with a homozygous pathogenic mutation in *MTFMT* who developed adult-onset LS.

Pathogenic mutations in the *MTFMT* gene were first reported in 2 children, aged 5 and 9 years, with LS and combined

**Table** Spectrophotometric analysis of the activities of the OXPHOS complexes in skeletal muscle and cultured skin fibroblasts in the proband and in the healthy controls

Complex	I	II	II + III	III	IV	V	CS
<b>Skeletal muscle homogenate</b>							
Proband	4	27	18	46	40	ND	94
<b>Controls</b>							
Mean	29	34	33	96	167	ND	174
P5-P95	15-52	18-58	18-50	50-145	82-266	ND	92-273
<b>Cultured skin fibroblasts</b>							
Proband	ND	27	32	42	44	ND	82
<b>Controls</b>							
Mean	ND	15	17	47	69	ND	82
P5-P95	ND	12-21	11-30	28-67	48-96	ND	59-109

Abbreviations: CS = citrate synthase; ND = not determined; OXPHOS = oxidative phosphorylation. All values expressed as nmol/min/mg protein.

OXPHOS deficiency.<sup>4</sup> To date, 22 patients with *MTFMT* mutations were reported in the literature. The age at onset varied between birth and 17 years. Most of them presented with ataxia, muscular hypotonia, and cognitive impairment, but recently reported cases support an expanding phenotypical spectrum, including MRI features mimicking demyelinating disease, cardiomyopathy, and even an association with renal dysplasia and moyamoya disease in a 4-year-old child.<sup>6,9-12</sup> Recently, a girl was reported with mild neurologic phenotype at age 7 years and involvement of the visual pathways starting at the age of 18 years.<sup>13</sup> *MTFMT*-patients with adolescent-onset symptoms are rare. They have developmental delay already present in childhood, slight intellectual disability, and behavioral problems.<sup>6,14</sup>

In the proband, molecular workup by WES and in silico analysis of the genes involved in mitochondrial transcription and translation revealed a homozygous missense mutation (c.626C>T, p.(Ser209Leu)) in the gene encoding *MTFMT*. This mutation is predicted to eliminate 2 overlapping exonic splicing enhancers (GTCAA and TCAAGA) and to generate an exonic splicing suppressor (GTTGTT) causing loss of function through altered splicing, leading to skipping of exon 4 and introduction of a premature stop codon resulting in truncation of the protein (p.Arg181Serfs\*5) as reported earlier.<sup>4,15</sup> The c.626C>T variant is present in the heterozygous state in 0.1% of the European population, making it a strong candidate gene for patients presenting with LS in combination with combined OXPHOS deficiencies involving complexes I and IV.<sup>6</sup>

The clinical course of LS in the proband initially seemed to be self-limiting and benign. Of interest, the proband developed an extrapyramidal syndrome within 2 years after onset of LS characterized by symmetrical parkinsonism signs with limited levodopa responsiveness, distinguishing it from classical

Parkinson disease (PD). Parkinsonian symptoms in *MTFMT*-deficient patients have not been reported so far. In most of the cases with adult-onset LS, EPS were limited to dystonia.<sup>16</sup> In only 1 report, extrapyramidal rigidity was described in an adult with LS. However, the molecular defect was not specified.<sup>17</sup> In the reported participant, EPS developed after stabilization of the symptoms attributed to LS, as was the case in the proband reported here. Juvenile parkinsonism with beneficial effect of treatment with levodopa was reported in an adolescent with Leigh-like phenotype caused by a point mutation in the mitochondrial tRNA<sup>Ile</sup> (m.4296G>A).<sup>18</sup>

To evaluate the dopaminergic system in the proband, FP-CIT SPECT and C-11 raclopride PET were performed. Symmetrical decreased density of presynaptic dopamine transporter terminals with bilaterally reduced FP-CIT binding was found. C-11 raclopride PET labeling of dopamine D2 receptors showed severe bilateral neostriatal reduction of C-11 raclopride, revealing postsynaptic dopaminergic impairment. This result is similar to that seen in the atypical parkinsonian syndromes, such as multiple system atrophy or progressive supranuclear palsy.<sup>19</sup>

Limited evidence on dopamine transport imaging in LS is available. A study on <sup>123</sup>I-FP-CIT striatal binding in 14 patients (age 35-69 years, median 48 years) with mitochondrial disorders and complex I deficiency failed to demonstrate dopaminergic cell loss. However, none of these patients suffered from LS or showed clear signs of parkinsonism.<sup>20</sup> In the participant reported here, cystic lesions in the neostriatum reflecting basal ganglia degeneration caused by mitochondrial dysfunction are likely to be involved in EPS. Of interest, a recent study on the etiologic role of epigenetic influences in PD showed a role of several microRNAs involved in a network of genes associated with PD. It was shown that the expression

of *MTFMT* (influenced by miR-488) was downregulated in the cingulate gyrus of patients with PD as compared to healthy controls. Dysregulation of 1 or more of the genes in the PD-genetic network, including *MTFMT*, might interfere with extrapyramidal neuronal integrity and function.<sup>21</sup> The findings in the participant described here provide additional clinical evidence for the hypothesis that *MTFMT* is involved in PD-related genetic network and that *MTFMT* dysregulation might be an etiologic factor in parkinsonism.

We cannot rule out that the older age of the proband as compared to other reported patients may have played a role in the development of atypical parkinsonism. At present, it is unclear whether parkinsonism is part of the *MTFMT* phenotype. Natural history data on patients with *MTFMT* mutations and advanced age are lacking. Our data suggest that dopaminergic neurons in patients with LS caused by pathogenic *MTFMT* mutations may be more susceptible to PD because of the impaired OXPHOS system, ultimately leading to a clinically significant extrapyramidal syndrome.

Adult-onset LS can be seen in patients with c.626C>T mutation in *MTFMT*. We showed that the affected patient had a defect in the dopaminergic system associated with atypical parkinsonism. Further research on the natural history of patients with pathogenic *MTFMT* mutations is needed to clarify the full clinical spectrum and underlying physiopathologic mechanisms.

### Author contributions

Each author listed in the manuscript has participated in editing the manuscript, has seen and approved the submission of this version of the manuscript, and takes full responsibility for the manuscript. In addition, A. V. Vanlander, T. Sante, E. Vantroys, and B. Menten conducted, analyzed, and interpreted the whole exome sequencing experiments; D. M. Hemelsoet and A. V. Vanlander acquired and analyzed phenotypic data; J. Smet acquired and processed all patient samples and analyzed data. A. V. Vanlander, S. Seneca, and B. Menten performed and interpreted Sanger sequencing. J. Smet and T. Sante contributed to study design and data analysis. M. Acou and I. Goethals were responsible for analysis of MR, PET, and SPECT imaging data and provided images for figure. D. M. Hemelsoet and R. Van Coster were responsible for primary study oversight and design, data acquisition, data analysis and interpretation, and primary writing of the manuscript. D. M. Hemelsoet and R. Van Coster are responsible for the overall content of the manuscript.

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