Clinical and molecular findings in a patient with a novel mutation in the deafness–dystonia peptide (DDP1) gene

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Summary

The Mohr–Tranebjaerg syndrome (MTS) is a rare neurodegenerative disorder characterized by early-onset deafness, dystonia and further neurological abnormalities such as cortical blindness, spasticity, dementia and mental retardation. Causative mutations were identified within the deafness–dystonia peptide (DDP1/TIMM8a) gene on the X-chromosome. The DDP1 protein is located in the intermembrane space of human mitochondria. Here, it acts in a complex together with its partner protein Tim13 in a chaperone-like manner to facilitate the import of nuclear-encoded precursor proteins into the mitochondrial inner membrane. Thus, MTS is a novel type of mitochondrial disorder. To obtain more insight into the pathophysiology of this neurodegenerative disorder, we performed for the first time a comprehensive clinical and functional characterization of a patient suffering from MTS. This patient exhibited a typical combination of deafness, dystonia and visual loss. Sequence analysis of the patient’s DDP1 gene revealed a G to C transversion at nucleotide position 38 of the first exon. The mutation affects the ATG start codon, thereby changing methionine to isoleucine (M1I), and leads to a complete absence of the DDP1 protein. In addition, the partner protein Tim13 was found to be significantly reduced, suggesting that Tim13 requires the presence of DDP1 for its stabilization. The assessment of mitochondrial functions showed the enzyme activities of the mitochondrial energy-generating systems to be normal in the muscle biopsy. Structural abnormalities or aggregations of mitochondria were absent. Electron microscopy revealed only a mild neurogenic atrophy. Neurophysiological investigations showed cochlear dysfunction and disturbance of visual pathways. PET and MRI studies revealed a multifocal pattern of neurodegeneration with hypometabolic areas predominantly located over the right striatum and parietal cortex and marked atrophy of the occipital lobes. Although the visual loss is caused predominantly by neurodegeneration of the visual cortex, degeneration of the retina and the optic nerve contributes to the visual impairment. The pathological changes in basal ganglia and sensory cortex demonstrate the disintegration of subcortical-cortical circuits and correlate well with the clinical presentation of multifocal dystonia. The data presented here showed that, in contrast to most of the known mitochondrial disorders, MTS appears not to be associated with a functional defect of the energy generation system of the mitochondria. Whereas the specific mitochondrial dysfunction leading to neuronal loss in MTS remains to be clarified, the electrophysiological and neuroimaging findings allowed the multifocal manifestation of neurodegenerative lesions in MTS to be characterized specifically.

Keywords: Mohr–Tranebjaerg syndrome; deafness–dystonia peptide (DDP1); progressive neurodegeneration; TIMM8a gene; mitochondrial pre-protein import

Abbreviations: AEP = brainstem auditory evoked potential; COX = cytochrome c oxidase; DDP1 = deafness–dystonia peptide 1; FDG = [18F]fluoro-2-deoxy-D-glucose; MEP = motor evoked potential; MTS = Mohr–Tranebjaerg syndrome; NCP = non-collagenous protein; OXPHOS = oxidative phosphorylation; PDH = pyruvate dehydrogenase complex; SEP = somatosensory evoked potential; TIM = translocase of the inner membrane; VEP = visual evoked potential

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Introduction

Mohr–Tranebjaerg syndrome (MTS) (also named deafness–dystonia syndrome) is a rare X-linked recessive deafness syndrome associated with dystonia and other neurological abnormalities (Mohr and Mageroy, 1960; Tranebjaerg et al., 1995). Early-onset progressive sensorineural hearing loss and dystonia are the only obligatory clinical symptoms. In some cases, visual loss can be found, while other patients never show signs of visual impairment even in old age (Swedlow and Wooten, 2001; Ujike et al., 2001). In addition, psychiatric symptoms, cognitive impairment and behavioral problems (Tranebjaerg et al., 1995, 1997) are observed frequently at later stages of the disease. In general, there seems to be a high degree of phenotypic variability.

The disease locus was mapped to the long arm of the X-chromosome by Tranebjaerg et al. (1995), and disease-causing mutations were found in a small novel gene on Xq22, subsequently named DDP1/TIMM8A (deafness–dystonia peptide 1) (Jin et al., 1996). Each of the MTS families harbour private mutations in the DDP1/TIMM8A gene. These include loss-of-function mutations such as frameshifts (151delT, 183del10 and 108delG) (Tranebjaerg et al., 1995; Jin et al., 1996; Swedlow and Wooten, 2001) and stop mutations (G105T→E24X and C273T→R80X) (Tranebjaerg et al., 1997; Ujike et al., 2001) all leading to an absence of the gene product. Only one missense mutation (C233G→C66W) (Tranebjaerg et al., 2000b) is known, so far.

The DDP1 gene encodes a small polypeptide of 97 amino acid residues. By homology searches, the DDP1 protein has been shown to belong to a family of evolutionarily conserved proteins located in the mitochondrial intermembrane space (Bauer et al., 1999; Koehler et al., 1999). MTS is, therefore, a novel mitochondrial disorder.

Functional studies on DDP1 and its yeast homologue Tim8 revealed a role in the import and insertion of newly synthesized precursor proteins into the mitochondrial inner membrane (Koehler et al., 1999; Paschen et al., 2000; Rothbauer et al., 2001; Roesch et al., 2002). In human mitochondria, DDP1 forms a hetero-oligomeric complex with a partner protein Tim13. Both act in a chaperone-like manner to stabilize the precursors of the hydrophobic inner membrane proteins during translocation across the aqueous environment of the intermembrane space.

Knowledge about the genetic defect and its functional characterization has increased the number of newly identified MTS cases. Whereas the description of the clinical features and their variability has become more precise during the past years, a profound in vivo characterization of this syndrome involving the state-of-the-art spectrum of electrophysiological and neuroimaging investigations is missing. Here, we present for the first time a detailed clinical characterization of an MTS patient, including comprehensive neurophysiological, neuroimaging, laboratory and metabolic investigations.

Patient and methods

Case report

The 41-year-old patient began suffering from hearing loss starting at 3 years of age. At 28 years of age, he developed a focal task-specific dystonia with myocloni in the left hand; these symptoms have deteriorated to a cervical dystonia and left-sided pronounced multifocal dystonia. At the age of 37 years, the patient developed a progressive impairment of visual acuity. Medication trials to treat his dystonia included baclofen, carbachazepine, clomipramine, sulpiride, L-dopa, trihexyphenidyl and tiapride, all without any effect. The dystonia has improved with propranolol and clonazepam; however, these drugs were stopped because of side effects. The family history is negative; the patient’s son (8 years old) and daughter (5 years old) are healthy.

On physical examination, the patient showed deafness and subsequent dysarthria, reduced visual acuity, with 0.2 for the right eye and 0.25 for the left eye, and bilateral mild temporal pallor of the optic discs. He had mild cranial dystonia, with the head habitually tilted and turned towards his left shoulder, with slight hypertrophy of the sternocleidomastoid and trapezius muscles. The left scapula was mildly winged. Brief bursts of myocloni were noted in the left sternocleidomastoid, in the deltoid and in the pectoralis muscles. Taking a full glass of water to the mouth and writing triggered a pronounced dystonic mass movement, with hyperextension of the wrist and raised shoulder accompanied by a dystonic abduction of the opposite arm; this pattern was intensified when the patient performed these tasks with his left hand. While walking, both arms showed dystonic abduction, more pronounced on the left side. When descending a flight of stairs without a handrail, a dystonic supination of the left foot occurred. The lower limbs showed a slight spasticity, and deep tendon reflexes were brisk without pareses or Babinski’s signs. Heel–knee–shin testing showed mild ataxia more pronounced on the left side.

The patient scored 34 out of 80 points in the severity score and duration score of the Unified Dystonia Rating Scale (Comella et al., 1998) and 42 out of 120 points in the dystonia movement scale and disability scale of the Burke–Fahn–Marsden Scale (Burke et al., 1985). His score in the Mini-Mental Status Examination was 30 out of 30.

Molecular genetics and biochemical analysis

Blood samples, a skin biopsy and muscle tissue taken from the lateral vastus muscle were analysed after informed consent was given by the patient. DNA was extracted from blood leucocytes according to standard purification protocols (Qiagen Inc., Germany). Exon 1 and exon 2 of DDP1 were PCR amplified using primer pairs (Ex1F) 5’-cggtgcgg-agtgcgctc-3’/(Ex1R) 5’-taagggtgctgcagg-3’ and (Ex2F) 5’-cgtttttttcagtccagtcg-3’/(Ex2R) 5’-tateccataacagctct-3’, and sequenced using a BigDye® Terminator Cycle Sequencing Kit (PE Applied Biosystems, Langen, Germany).
Total RNA was extracted from cultured skin fibroblasts by standard procedures (TRIZOL®, Life Technologies) and reverse transcribed using Superscript II reverse transcriptase (Life Technologies) and oligo d(T) primers. PCR was performed using DDP1- and Tim13-specific primers as described previously (Rothbauer et al., 2001), and GAPDH-specific primers as a control.

To determine steady-state protein levels of DDP1 and Tim13, crude extracts from myoblast cells (1 × 10^5 cells) were separated on 15% SDS-polyacrylamide gels and analysed by western blotting using polyclonal antibodies against human DDP1 and Tim13 (Rothbauer et al., 2001). As a control, immunodecorations were performed with antibodies against β-actin (Sigma Inc., Taufkirchen, Germany).

In addition, material from open muscle biopsy was used for enzyme biochemistry and histochemistry. Enzymatic activities of complexes I (NADH-CoQ oxidoreductase), II (succinate/cytochrome c oxidoreductase) and IV [cytochrome c oxidase (COX)] of the mitochondrial respiratory chain and the pyruvate dehydrogenase (PDH) complex were determined using a coupled spectrophotometric assay in the post-nuclear supernatant of the fresh-frozen skeletal muscle biopsy as described previously (Fischer et al., 1986). Activities were expressed as units per gram of non-collagenous protein (U/g NCP) and related to the mitochondrial marker enzyme citrate synthase.

Results

Molecular genetic characterization

Most of the patients with MTS reported so far harbour loss-of-function mutations. The sequence analysis of the patient presented here revealed a novel G to C transversion at nucleotide position 38 in the first exon of the DDP1/TIMM8a gene. The G38C mutation represents a de novo mutation since it was not detectable in blood DNA samples from the healthy mother and sister of the patient. The 5-year-old daughter of the patient could not be tested but will be a heterozygous carrier of the G38C mutation. The mutation changes the coding triplet to ATC, thereby changing methionine (ATG) to isoleucine (ATC). The translation initiation codon of the DDPI gene affects the start codon of DDP1, thereby changing methionine (ATG) to isoleucine (ATC). Nucleotide position 1 corresponds to the first base of exon 1.

Both genes DDP1 and Tim13 were found to be expressed normally at the mRNA level (Fig. 2B). Thus, reduced amounts of Tim13 protein are caused by protein degradation rather than by downregulation or instability of mRNA transcripts.

Neurophysiological and neuroimaging studies

Brainstem auditory evoked potentials (AEPs) were bilaterally absent (I and II) or showed prolonged (III–V) peaks, thus indicating cochlear dysfunction, rather than involvement of the brainstem. Visual evoked potentials (VEPs) were prolonged for the right eye and absent for the left eye. Somatosensory evoked potentials (SEP) of the median and tibial nerves showed markedly prolonged central sensory
conduction time. Transcranial magnetic stimulation to determine motor evoked potentials (MEPs) revealed disturbed central motor conduction to the lower extremities, but not to the upper extremities. Motor and sensory nerve conduction studies and electromyography were normal.

The cranial MRI showed marked cortical atrophy of both occipital and rostral parietal lobes (Fig. 3). There were no abnormalities in the basal ganglia, white matter or the remaining cortex. The $^{18}F$fluoro-2-deoxy-D-glucose (FDG) PET qualitatively showed a pronounced reduction of metabolism in both occipital lobes including the visual cortex, but also in the basal ganglia and both rostral parietal lobes (Fig. 3).

**Functional and morphological examinations**

The activities of the mitochondrial respiratory chain enzymes NADH-CoQ oxidoreductase (complex I), succinate–cytochrome $c$ oxidoreductase (complex II and III) and COX (complex IV) in post-nuclear supernatants prepared from frozen muscle tissue were at the upper limit of the normal range. The activities were as follows: NADH/CoQ oxidoreductase, 33.3 U/g NCP (reference range: 12.0–26.4 U/g NCP); succinate/cytochrome $c$ oxidoreductase, 17.3 U/g NCP (6.0–25.0 U/g NCP); COX, 253 U/g NCP (90–281 U/g NCP). When expressed as ratios referred to the mitochondrial marker enzyme citrate synthase (99 U/g NCP; reference range 45–100 U/g NCP), the activities of all four respiratory chain complexes were within the normal range. The PDH activity was normal at 2.2 U/g NCP (1.5–3.9 U/g NCP).

Similarly, the patient showed normal complex IV staining when enzymatic histochemistry was performed. No COX-negative or ragged-red fibres were seen. Electron microscopic examination of the patient’s muscle biopsy was indicative of mild neurogenic atrophy. Some single fibres showed a slight subsarcolemmal aggregation of mitochondria. No ultrastructural changes such as thickened or abnormal mitochondrial cristae or mitochondria of abnormal shape or sizes were detected. Furthermore, routine laboratory analytes and metabolic parameters such as pyruvate, lactate and amino acids, and acetyl carnitines in serum as well as organic acids in the urine were found to be within the reference ranges.

In summary, laboratory and histological investigations did not reveal a specific mitochondrial dysfunction in the material investigated. In particular, the loss of DDP1 does not affect the energy-generating system (oxidative phosphorylation; OXPHOS), nor does it cause a block in metabolic pathways of the substrate oxidation located in the mitochondria.

**Discussion**

MTS is a novel type of mitochondrial disorder caused by mutations in the DDP1 gene on the X-chromosome. Progressive neurodegeneration leads to sensorineural hearing loss, dystonia and a variety of non-obligatory neurological features.

The patient presented here shows post-lingual early-onset deafness, progressive multifocal, task-specific dystonia and beginning visual loss. The combination of symptoms and the order of onset in our patient are typical for MTS; however,
Table 1  Clinical features of published MTS cases with mutations in the DDP1 gene

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients (age range)</th>
<th>Patients with deafness (age of onset)</th>
<th>Patients with dystonia (age of onset)</th>
<th>Patients with visual loss (age of onset)</th>
<th>Other symptoms</th>
<th>Gene defect</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohr and Mageroy (1960),</td>
<td>12 (11–54 years)</td>
<td>12 (2–11 years)</td>
<td>8 (~50 years)</td>
<td>9 (~40 years)</td>
<td>Mild peripheral neuropathy, mental deterioration, fractures, generalized atrophy in CT scans, one patient died at 16 years of age</td>
<td>151delT</td>
<td>Frameshift</td>
</tr>
<tr>
<td>Tranebjærg et al. (1995),</td>
<td>5 (not reported)</td>
<td>Yes, no further details reported</td>
<td>Yes, no further details reported</td>
<td>Yes, no further details reported</td>
<td>Mental deficiency; three patients died at 10, 34 and 40 years of age</td>
<td>183del10</td>
<td>Frameshift</td>
</tr>
<tr>
<td>Tranebjærg et al. (2000a)</td>
<td>3 (not reported)</td>
<td>3 (1–1.5 years)</td>
<td>2 (14–21 years)</td>
<td>1 (19 years)</td>
<td>Progressive disturbance of mental function</td>
<td>G105T</td>
<td>Stop</td>
</tr>
<tr>
<td>Swerdlow and Wooten (2001)</td>
<td>1 (11 years)</td>
<td>2.5 years</td>
<td>10 years</td>
<td>No</td>
<td>Hyper-reflexia, dyspraxia, synkinesia</td>
<td>C233G</td>
<td>Missense</td>
</tr>
<tr>
<td>Ujike et al. (2001)</td>
<td>5 (15–89 years)</td>
<td>5 (0.5–9 years)</td>
<td>4 (16–30 years)</td>
<td>37 years</td>
<td>Mild mental deterioration</td>
<td>C273T</td>
<td>Stop</td>
</tr>
<tr>
<td>This study</td>
<td>1 (41 years)</td>
<td>3 years</td>
<td>28 years</td>
<td>No</td>
<td>No</td>
<td>G38C</td>
<td>Missense</td>
</tr>
</tbody>
</table>

compared with other published cases, dystonia appeared relatively late in his life (Table 1).

The diagnosis of MTS in our patient was confirmed by the identification of a novel de novo mutation within the DDP1 gene. This mutation, G38C, affects the translation initiation codon of DDP1, changing methionine (ATG) to isoleucine (ATC). Most of the DDP1 gene mutations described so far are loss-of-function mutations leading to absent or truncated proteins. Only two missense mutations in DDP1/TIMM8a are known: (i) an amino acid exchange from cysteine to trytophan (C66W) (Tranebjærg et al., 2000a) affecting a highly conserved metal-binding motif; and (ii) the M1I mutation described in the present study. Both missense mutations exhibit the same effect as typical loss-of-function mutations, as they cause an absence of the gene product: the DDP1 protein carrying the C66W mutation has been shown to be degraded rapidly due to its improper state of folding (Hofmann et al., 2002; Roesch et al., 2002), whereas the M1I mutation is shown to completely abolish translation initiation of DDP1 in our patient.

In the intermembrane space of human mitochondria, DDP1 forms a stoichiometric hetero-oligomeric complex with its cognate partner protein Tim13 (Rothbauer et al., 2001). DDP1 and Tim13 show a marked sequence similarity; however, they cannot functionally substitute for each other. Here we show that the absence of DDP1 in the cells carrying the M1I mutation influences the steady-state levels of Tim13. In DDP1-deficient myoblasts, Tim13 is markedly reduced compared with a normal control. This indicates that Tim13 requires DDP1 as partner protein for its stability. This view is supported by observations in yeast and mammalian cells expressing the C66W mutation in which Tim13 becomes degraded in the absence of DDP1 (Hofmann et al., 2002; Roesch et al., 2002).

Typically, mitochondrial disorders are caused by dysfunction of the energy-generating system, i.e. the respiratory chain coupled to oxidative phosphorylation (OXPHOS). Diagnosis of mitochondrial disorders is based on the measurement of enzyme activities of the OXPHOS complexes often in combination with laboratory, morphological and histochemical findings. The cellular pathomechanism by which the loss of DDP1 leads to progressive neurodegeneration in MTS is completely unknown, so far. The DDP1–Tim13 complex has been shown to assist the import of hydrophobic precursor proteins into the mitochondrial inner membrane (Rothbauer et al., 2001; Roesch et al., 2002). The OXPHOS system is located in the inner membrane, and components of the OXPHOS complexes were, therefore, considered as potential substrates of the DDP1–Tim13 complex. However, the enzyme activities of the respiratory chain were found to be within the normal range in the patient’s muscle. Thus, the absence of functional DDP1–Tim13 complexes appears not to affect the biogenesis and performance of the OXPHOS system, in neither a direct nor an indirect manner. It cannot be excluded that the consequences of the loss of DDP1 on mitochondrial function are absent in non-neuronal cells. Therefore, further attempts are necessary to identify substrates of the DDP1–Tim13 complex in order to characterize the specific mitochondrial dysfunction underlying MTS.

The pattern of the clinical features in MTS suggests a multifocal neurodegeneration affecting distinct areas of the CNS. However, neuroimaging studies assessing the MTS-
specific alterations are rare. The data published so far revealed unspecific alterations in CT scans, such as diffuse, generalized cerebral or cortical atrophy (Jensen et al., 1987; Tranebjaerg et al., 1995) which cannot account for the clinical signs described in these patients. The results of a first PET study exhibited hypometabolic areas over parietal, medial temporal and frontal brain areas (Tranebjaerg et al., 2001). More detailed findings in MTS patients are based mainly on post-mortem investigations (Merchant et al., 2001; Tranebjaerg et al., 2001). In particular, diffuse gliosis in the globus pallidus and a massive reduction of spiral ganglion cells of the inner ear were found to be histopathological correlates of the dystonia and deafness, respectively. Neuropathological alterations corresponding to the visual loss seem to involve not only the visual cortex but mainly peripheral visual structures, in particular the retinal neurons and the optic nerve fibres. In addition, atrophy and loss of fibres in dorsal roots and posterior columns were suggested to cause spinal cord dysfunction.

This study presents the first detailed functional in vivo investigation of a patient with MTS combining evoked potentials studies (AEPs, VEPs, SEPs and MEPs) and neuroimaging techniques (PET and MRI). Hearing impairment in our patient suggested deafness of the cochlear type (absence of peaks I and II); an involvement of the brainstem appears to be unlikely (presence of peaks III–V). The unremarkable pattern of the temporal cortex visualized by MRI and PET also supports the cochlear system rather than the brainstem and the auditory cortex to be affected primarily by the neurodegenerative process.

Markedly prolonged or even absent VEPs reflect a severe disturbance of visual pathways. Recent neuropathological findings in MTS patients showed impairment of peripheral visual structures, in particular degeneration of retinal neurons and optic nerve fibres (Merchant et al., 2001; Tranebjaerg et al., 2001). Our patient, however, demonstrates a marked occipital hypometabolism in PET and a bilateral atrophy in MRI. Thus the major contribution to visual loss seems to be degeneration of central visual components. A trans-synaptic degeneration secondary to peripheral visual damage is unlikely because of the extended cerebral hypometabolism and atrophy which spread beyond the primary visual cortex. This hypothesis is supported by studies demonstrating normal cerebral, particularly occipital morphology in MRI in patients with congenital peripheral neuronal dysfunction caused by retinal and optical nerve degeneration (Breitenseher et al., 1998).

The more pronounced left-sided dystonic symptoms in our patient correlate well with the distribution of hypometabolic regions in the basal ganglia, present to a greater extent in the right hemisphere, particularly in the striatum, and in both parietal cortices. This pattern reflects both basal ganglia dysfunction and sensorimotor disintegration due to disturbed cortico-subcortical circuits, respectively, which is in line with current concepts on the pathophysiology of dystonia (Berardelli et al., 1998). Whereas in primary dystonia FDG-PET findings are inconclusive (Chase et al., 1988; Karbe et al., 1992; Otsuka et al., 1992), in heredodegenerative dystonia–parkinsonism syndromes, reduced striatal glucose metabolism has been reported frequently (Filipino X-linked dystonia parkinsonism, (Eidelberg et al., 1993) or X-linked McLeod syndrome (Jung et al., 2001)). Compared with post-lesional dystonia, e.g. due to basal ganglia ischaemia (Kryskowiak et al., 1998), pathological MRI changes in primary or heredodegenerative dystonia are rare (Rutledge et al., 1988) or only detectable by special imaging methods, e.g. high field studies (Schneider et al., 1994). Routine MRI in our patient showed no pathological findings in the basal ganglia. Thus, the typical imaging findings of heredodegenerative dystonia are present.

Furthermore, spinal cord dysfunction was assumed on the basis of a mild spasticity and minor ataxia of the lower limbs. This was supported by disturbed central motor conduction to lower extremities in MEPs and prolonged central sensory conduction time in SEPs.

In summary, we report a patient with MTS showing deafness and dystonia as the typical symptoms and visual loss as an additional feature. Electrophysiological and neuroimaging investigations revealed specific delayed conduction times, multifocal lesions within subcortico-cortical circuits and a marked degeneration of occipital lobes. Localization and the extent of the lesions correlate well with the clinical symptoms. The diagnosis of MTS was confirmed by the identification of a novel de novo missense mutation in the DDP1 gene causing the absence of the DDP1 protein in the patients’ mitochondria. So far, the specific mitochondrial dysfunction is unclear and the mechanisms by which loss of DDP1 function leads to neurodegeneration within specific brain areas remain to be unravelled.

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