RESEARCH ARTICLE

The Phenotypic Spectrum of Dystonia in Mohr–Tranebjaerg Syndrome

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ABSTRACT: Mohr–Tranebjaerg syndrome (MTS) is an X-linked recessive disorder characterized by deafness and dystonia. However the phenotypic expression of dystonia has not been systematically defined. We report clinical, neurophysiological, and ophthalmological data on 6 subjects from 3 Australian kindreds, including 2 with novel mutations, together with a systematic review of the literature, in order to define the phenotypic expression of dystonia. Profound hearing impairment in affected males develops by infancy and precedes the development of dystonia, which varies in time of onset from the first to the sixth decades, with a peak in the second and third decades. Dystonia in MTS tends to be focal, segmental, or multifocal in distribution at onset, with a predilection for the upper body, variably involving the head, neck, and upper limbs. The majority of patients have progression or generalization of their dystonia regardless of age of onset. Within our 3 kindreds, we observed relative intrafamilial homogeneity but interfamilial variation. The median time to the development of moderate-severely disabling dystonia in these subjects was 11 years. Associated features included progressive cognitive decline, pyramidal signs, and in 1 patient, gait freezing and postural instability. Optic atrophy and cortical visual impairment were both observed. We report for the first time a female patient who developed multiple disabling neurological complications of MTS. Our findings more clearly define and expand the phenotype of both the dystonia and other neurological features of MTS and have implications for the diagnosis and management of this condition.

Key Words: Mohr–Tranebjaerg syndrome; deafness-dystonia-optic neuronopathy (DDON) syndrome; generalized dystonia; *TIMM8A*; sensorineural hearing impairment

Mohr–Tranebjaerg syndrome (MTS; MIM 304700), or deafness–dystonia–optic neuronopathy (DDON) syndrome, is an X-linked recessive disorder resulting from loss-of-function mutations in the nuclear-encoded deafness dystonia peptide 1 (*DDP1*)/translocase of mitochondrial inner membrane 8A (*TIMM8A*) gene (MIM 300356), located at Xq22.1.[1,2] MTS was first reported as nonsyndromic X-linked deafness (DFN-1) in 1960,[1,3] with the recognition that dystonia was an integral part of the condition occurring later.[1,2]

To date, only 32 unrelated individuals have been identified with mutations in *TIMM8A* encoding a 97-amino-acid protein. Point mutations and partial, whole, and contiguous gene deletions have been described.[4] There is considerable clinical heterogeneity in this syndrome, with both intrafamilial and

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Additional Supporting Information may be found in the online version of this article.

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interfamilial phenotypic variation described.[2,4,5] The presence of deafness and dystonia appear to be consistent features of the disease, whereas features of ataxia, spasticity, cognitive impairment, psychiatric disease, and optic atrophy show greater variability.[5]

The phenotypic expression of dystonia in MTS has not been systematically studied. We report clinical, neurophysiological, ophthalmological, and genetic data from 6 genetically proven MTS patients and 3 relatives from 3 unrelated Australian kindreds, including follow-up data and genetic confirmation on a previously reported kindred.[6] From review of our patients and the literature, we define the phenotypic expression of dystonia in MTS in order to assist in the diagnosis and management of this syndrome.

Patients and Methods

Patients

Three patients with a history suggestive of MTS presenting to a tertiary movement disorders clinic in Sydney, Australia, between 1992 and 2002 were examined, and mutations were found in *TIMM8A*. First-degree family members of index patients with or without a history suggestive of hearing impairment (HI) or dystonia were invited for clinical and genetic assessment. Informed consent was obtained from all participants.

Sequence Analysis

We designed primers to amplify the 2 exons and surrounding intronic regions of *TIMM8A* (RefSeq NM_004085.3) by PCR. Primer sequences and PCR conditions are available on request. PCR products were sequenced using BigDye Terminator Kit version 1.1 (Applied Biosystems, Foster City, CA, USA) and separated on an ABI 3130 XL genetic analyser (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions. Identified changes in the nucleotides were checked against databases of published polymorphisms and mutations (http://www.hgmd.cf.ac.uk/ac/index.php). We used sequencing to study the segregation of the mutations with the disease in each family.

Literature Review

Previously reported cases of MTS were ascertained using Pubmed searches for articles using the key words "Mohr-Tranebjaerg syndrome," "deafness AND dystonia," "deafness dystonia peptide," and "deafness dystonia syndrome," as well as reference lists from previously published articles, and analyzed for data regarding the characteristics of the dystonia and genetic mutations.

Results

The details of each pedigree are shown in Figure 1. Three probands (2 male, 1 female) were confirmed as having pathogenic mutations in *TIMM8A*. An additional 6 first-degree relatives with a clinical history suggestive of MTS were identified. Of these, 2 patients were deceased, and 1 declined further investigation. Accordingly, a total of 6 subjects were reviewed.

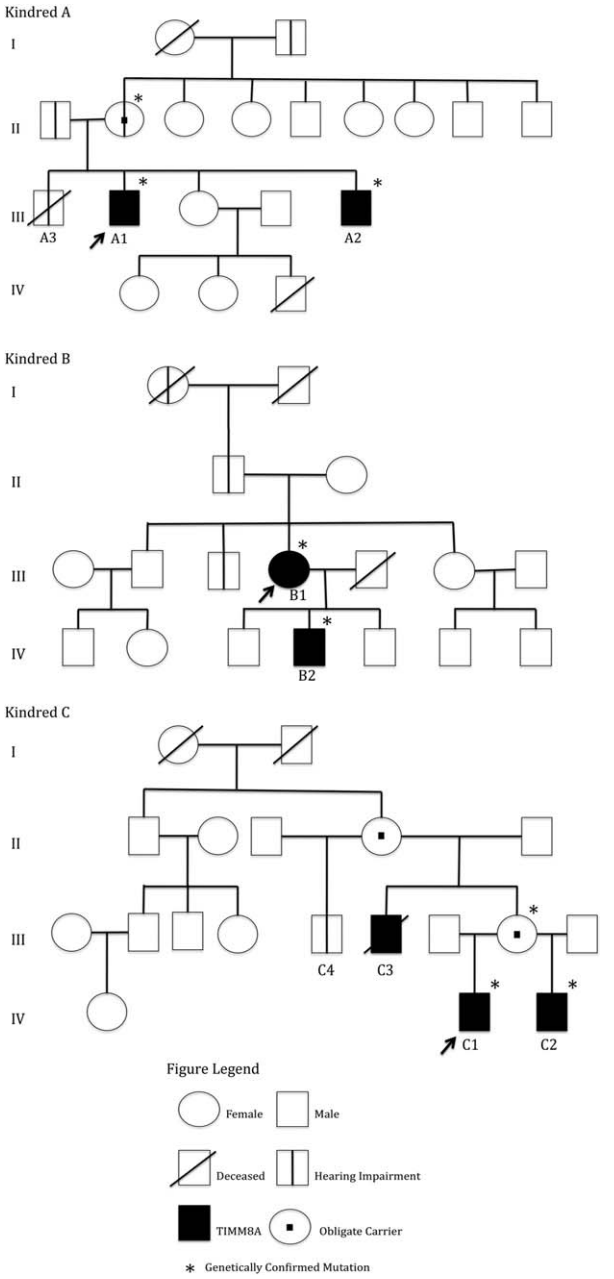

FIG. 1. Pedigrees of kindreds A, B, C. Note that in kindred B, in addition to genetically proven MTS, there was also a paternal history of deafness in the proband.

Clinical Features

The clinical features of patients tested for genetic mutations (n = 6) and those additional patients with suspected MTS in whom genetic material was not obtained (n = 3) are presented in Table 1. More detailed information regarding the clinical presentation of these subjects is available in the Supplementary Material.

TABLE 1. Clinical and genetic features of kindreds A, B, C

Case	Sex	Age at onset of deafness	Age at onset of dystonia	Topography at onset	Anatomical progression	Time to progression to moderately-severely disabling dystonia (y)	Associated features (age at onset)	Identified *IMM8A* mutation
A1	Male	<2	30	Left upper limb	Upper limbs, right upper limb dystonic tremor, oromandibular, lower limbs	12	Optic atrophy (40) Dementia (early 50s)	Deletion of exon 2
A2	Male	<2	40	Tremulous cervical dystonia	Nil at 3 years	—	Optic atrophy (43)	Deletion of exon 2
A3	Male	<2	—	—	—	—	—	Not tested
B1	Female	Early 40s	Mid-40s	Right upper limb (writer's cramp)	Oromandibular, upper limbs, lower limbs	10	Cognitive decline (50s) Pyramidal signs (54) Gait freezing (59)	c.127delT; p.Cys43ValfsX22

(Continued)

Deafness and Dystonia

Profound HI always preceded dystonia in males but not in the female. Dystonia developed at a median age of 30 years (range, 6–45 years; n = 6). The exact site and type of dystonia at onset was variable but almost always in the upper half of the body rather than in the lower limbs.

Dystonia was progressive in most cases, both in topography and increasing severity. Of the 6 cases that we reviewed with genetically confirmed MTS, 5 developed dystonia. B2 had not shown signs of dystonia at age 30. Progression of dystonia occurred in 4 patients (A1, B1, C1, C2). Median time of progression to moderately-severely disabling dystonia, which we defined as loss of independence in at least 1 activity of daily living, was 11 years (range, 4–13 years). C-1 succumbed to complications of generalized dystonia.

Associated Features

Five patients had intellectual impairment or cognitive decline, with frontal-subcortical features such as impulsiveness and lack of insight into their impairment (Table 1). Two of the affected males in kindred C (C-1, C-2) also suffered from behavioral disturbance from childhood. Four patients (B-1, C-1, C-2, C-3) exhibited pyramidal signs. B-1 also developed features of parkinsonism, characterized by shuffling gait with start hesitation, freezing, and postural instability. A-1 demonstrated symmetrical caudate head atrophy on cranial magnetic resonance imaging (MRI).

Visual impairment was a notable feature in several members of the affected kindreds and was either a result of optic atrophy or, less commonly, cortical visual impairment. Further details are available in the Supplementary Materials.

Neurophysiology

The full results are presented in the Supplementary Materials. In brief, visual-evoked potentials (VEPs) and median and tibial somatosensory-evoked potentials (SSEPs) were abnormal in affected members in kindreds A and B.

Genetics

The *TIMM8A* gene was sequenced in 6 patients from 3 families. The full results are presented in the Supplementary Materials. In brief, affected members of kindred A had a novel mutation consisting of a deletion of exon 2, kindred B had a single base-pair deletion that was subsequently reported in a Spanish kindred,[7] and kindred C were found to have a novel nonsense mutation in exon 1.

Literature Review

Data regarding the clinical and genetic spectrum of dystonia in previously reported cases of MTS are summarized in Table 2. Together with the data from our

3 kindreds, we identified several trends in the distribution and progression of dystonia in MTS. First, whereas primary dystonia in adults typically remains focal,[8] in MTS there is a gradual progression of dystonia to multifocal, segmental or generalized forms, regardless of age of onset.[7,9–12] Second, there is a predilection for onset in the upper limbs or craniocervical region. Of the 22 cases previously reported in the literature with a description of topography at onset, 21 (95%) included upper limb or craniocervical onset, with or without lower-limb involvement,[5–7,9–18] although the characterization of dystonia was limited in some reports.

Although the number of published reports detailing dystonia in large families is limited, there is a trend toward intrafamilial similarity in the presentation and progression of dystonia. For example, affected members of our kindred C presented with dystonia at a young age, which progressed to severe generalized dystonia and eventual death/dependency. In contrast, in our kindred A, A-1, and A-2 both presented with a less severe dystonia phenotype characterized by adult-onset focal dystonia.

We also found evidence of interfamilial variation in the precise clinical phenotype between kindreds, even in families harboring the same mutation. The clinical features of B-2, who has not shown signs of dystonia at age 30, are markedly dissimilar to a previously described family with no established connection who had the same mutation, in which the proband developed dystonia at age 8.[7]

Discussion

Phenotypic Expression of Dystonia in MTS and Comparison with Other Dystonic Syndromes

Our study has demonstrated 3 findings of significance. First, there is a wide range of age of onset of dystonia in MTS, occurring most commonly in young adults in the second or third decade but ranging from juvenile onset (first decade) to late-adult onset (up to the sixth decade). Second, there is a predilection for onset in the craniocervical region or upper limbs, occurring in 95% of cases regardless of age of onset. This was evident even in those with childhood-onset dystonia, in contrast to the lower-limb distribution seen in childhood primary dystonia. Third, progression to moderate-severe disability is common over the course of approximately a decade, again regardless of age of onset.

Oromandibular dystonia, which was present in our female proband (B-1), may also be a feature of several other heredodegenerative conditions such as neuroacanthocytosis, neuroferrinopathy, and pantothenate kinase–associated neurodegeneration;[8] however, they are not typically associated with profound HI. Other secondary dystonia syndromes may also be accompanied by deafness.[8] Woodhouse–Sakati syndrome is an autosomal recessive neuroendocrine disorder with sensorineural deafness in which dystonia or chorea tend to present with focal limb onset in adolescence or adulthood.[19] In contrast to MTS, it is usually accompanied by other clinical findings such as seizures and endocrine and autoimmune disorders. Mitochondrial diseases have a varied clinical phenotype and may also manifest with features of deafness and dystonia.[20]

Relationship between Dystonia and Deafness in MTS

All *male* MTS patients reported to date who are affected with dystonia have had profound HI. The hearing impairment is sensorineural, in keeping with histopathological data demonstrating severe auditory neuropathy, with almost complete degeneration of cochlear neurons as well as extensive vestibular neuronal loss.[21] The onset of HI occurs in infancy and predates the dystonia by years to decades. In contrast, our female proband demonstrated only mild and clinically nondisabling HI, similar to a previously reported female subject with a mild focal dystonic phenotype without HI.[9]

Additional Clinical Features That Provide a Clue to Diagnosis of MTS

Associated neurological symptoms in MTS vary considerably in onset, severity, and rate of progression and include intellectual and behavioral disturbance, visual disturbance, pyramidal signs, and peripheral neuropathy. Neuropathologically, there are major neurodegenerative abnormalities in affected males at advanced adult age.[15]

Although visual disturbance in MTS is typically a result of optic atrophy, cortical visual disturbance may also occur. Cortical pathology has been reported previously in MTS,[16] and neuropathological studies have demonstrated neuronal cell death in the visual cortex.[15] The presence of neuronal loss and cortical atrophy, particularly affecting the occipital lobes, in addition to optic atrophy may form part of a widespread neurodegenerative process that affects several components of the visual pathway.[15]

Abnormalities were also seen in somatosensory-evoked potentials (SSEPs) in our series, in keeping with a previous case report.[16] These results suggest disturbance of the afferent somatosensory pathways in MTS, although additional studies are required to define the pathophysiological mechanisms underlying the SSEP abnormalities in MTS.

Features of Bruton agammaglobulinemia, or X-linked agammaglobulinemia, may also be present if the mutation involves a contiguous gene deletion

TABLE 2. Summary of previously reported clinical and genetic spectrum of dystonia in MTS

Source	Patients	Age at onset of deafness (y)	Dystonia	Age at onset of dystonia (y)	Topography at onset	Anatomical Progression (y)	Time to progression to marked disability	Mutation	Mutation[b]/ predicted effect
Scribanu et al, 1976	Proband	2	+	7	Writer's dystonia, limbs	Neck	2	Not identified	
	Maternal uncle	6	+	>6	NR	Generalized	18	Not identified	
Tranebjaerg et al, 1995	16 Cases		+ (8/12)	7–50	Variable	Variable	Variable	c.151delT	c.116delT/ Met39ArgfsX26
	10 Alive	2–7	4	NR					
Jin et al, 1996	5 Cases	NR	NR	NR	NR	NR	NR	c.183del10	c.148_157del/ p.Lys50GlnfsX12
Hayes et al, 1998[a]	Proband	<2	+	6	Upper limbs, trunk, cranial	Cervical, lower limbs	13	p.Gln18X	c.52C>T/p.Gln18X
	Half brother	<2.6	+	16–23	Cranial, cervical, upper limbs, lower limbs	Generalized	4	p.Gln18X	c.52C>T/p.Gln18X
	Maternal uncle	NR	+	NR	NR	Generalized	NR	Not tested	
	Maternal uncle	<2	NR	NR	NR	NR	NR	Not tested	
Tranebjaerg et al, 2000	Proband	2.5	+	10	Unilateral upper limb	NR	NR	c.233C>G	c.198C>G/ p.Cys66Trp
Tranebjaerg et al, 2001	Proband	2	− (at age 21)	—	—	—	—	c.105G>T	c.70G>T/p.Glu24X
	Maternal uncle	1.5	+	21	Cervical	NR	NR	Not tested	
	Maternal uncle	Early infancy	− (at age 21)	—	—	—	—	Not tested	
Swerdlow et al, 2001	Proband	Congenital	+	28	Head, cervical	Generalized	Unclear	c.108delG	c.73delG/p.Val25X
	Mother	—	+	25	Cervical, writer's dystonia	—	—	c.108delG	c.73delG/p.Val25X
	Sister	—	+	Teens	Cervical	Segmental	10	c.108delG	c.73delG/p.Val25X
	Maternal uncle	Congenital	+	Late 20s	Generalized	Generalized	NR	Not tested	
	Maternal uncle	Congenital	− (deceased age 22)					Not tested	
	Maternal great-grandmother	NR	+	NR	Neck	NR	NR	Not tested	
	Two maternal male second cousins	Early onset	+	Adult age	NR	NR	NR	Not tested	
Ujike et al, 2001	Proband	6 months	+	30	Upper limbs	Generalized	5	p.Arg80X	c.238C>T/p.Arg80X
	Brother	4	+	16	Multifocal	Generalized	13	p.Arg80X	c.238C>T/p.Arg80X
	Maternal grandfather	+ (age unknown)	+	NR	Lower limbs	NR	NR	Not tested	
	Maternal male cousin	3–4	+	Unclear	Generalized	Generalized	>30 (mild)	p.Arg80X	c.238C>T/p.Arg80X
	Maternal nephew	8–9	−	—	—	—	—	p.Arg80X	c.238C>T/p.Arg80X
Binder et al, 2003	Proband	3	+	28	Unilateral upper limb	Multifocal	13	c.38G>C	c.3G>C/p.Met1Ile
Pizzuti et al, 2004	Proband	2	+	19	Writer's dystonia	NR	NR	Deletion of *TIMM8A*	
Ezquerra et al, 2005	Proband	4	+	11	Writer's dystonia	Neck and foot, then generalized	7	IVS1-23A>C	IVS1-23A>C/ altered splicing
	Male cousin	11	+	20	Upper limbs	Generalized	9	IVS1-23A>C	IVS1-23A>C/ altered splicing
Aguirre et al, 2006	Proband	3.5	+	8	Upper limbs	Generalized	2	c.127delT	c.127delT/ p.Cys43ValfsX22
	Brother	7	−	—	—	—	—	c.127delT	c.127delT/ p.Cys43ValfsX22
Kim et al, 2007	Proband	8 months	+	25	Blepharospasm	Generalized	9	IVS1+1G>A	IVS1+1G>A/ altered splicing
Blesa et al, 2007	Proband	3	+	30	Neck	—	—	c.112C>T	c.112C>T/ p.Gln38X
Aguirre et al, 2008	Proband	4	+	23	Blepharospasm, facial grimacing	NR	NR	IVS1+1G>T	IVS1+1G>T/ altered splicing

NR, not reported.
[a]Case included in current report.
[b]According to recommended mutation nomenclature. Nucleotide numbering refers to the *TIMM8A* cDNA sequence NM_004085.3 in GeneBank with nucleotide number +1 being A of the start codon ATG.

disrupting *BTK* and, less commonly, *TAF7L* and *DRP2*.[22] The co-occurrence of X-linked hearing impairment and agammaglobulinemia should therefore raise the suspicion of MTS. In 1 case, a male patient with HI and immunodeficiency had a cochlear implant before it was realized that he suffered from MTS.[23] The occurrence of additional clinical symptoms from a neighboring gene deletion in the setting of a large gene mutation has been reported in other dystonia genes such as myoclonus-dystonia, in which deletion of the entire *SGCE* gene has been associated with collagen type I alpha 2 gene deletion, leading to additional phenotypic features.[24] Complete deletion of the *TIMM8A* gene with accompanying *BTK* deletion has been associated with a less severe dystonia phenotype than truncating mutations.[17] In our series, kindred A, whose affected individuals harbored a deletion of exon 2 mutation in *TIMM8A*, presented with focal dystonia that resembled the rather mild dystonia in a case of deletion of the entire *TIMM8A*.[17]

Female Expression of MTS

Female carriers with manifest disease have been described only rarely.[1,9] The clinical features of the female proband in kindred B expands the female phenotype of MTS, which usually manifests as an X-linked recessive disorder, to that of an almost full spectrum of neurological involvement including dystonia, cognitive decline, and predominantly cortical visual impairment, as well as the novel manifestation of parkinsonism and balance impairment. To our knowledge, this is the first reported female patient to develop multiple disabling neurological complications of MTS.

Genetics of MTS

Unique mutations have been identified in nearly all reported MTS families to date (Table 2), including 2 novel mutations from this study. Sporadic cases have been reported.[5,14] Several types of mutations including frame-shift, nonsense, and missense mutations and deletions have been identified.[11] Many of these mutations result in the formation of a premature stop codon, making it likely that these mutations lead to complete inactivation of the gene product.[7] The role of modifying genes has been postulated[5,7] and genes encoding other small TIMM proteins involved in import of proteins suggested.[7] If these genetic modifiers are unique to families, it may explain the interfamilial variation seen in the clinical phenotype.

Legends to the Video

Video Segment 1: Patient B1 at the time of presentation in 2002, aged 54. She has oromandibular dystonia mainly during speaking, which is improved by a sensory trick of lightly holding the angles of her jaw. She has normal posture when holding the limbs outstretched and performing fractionated finger movements, with some low-amplitude mirror movements. She has dystonic posturing when writing. Gait is within normal limits.

Video Segment 2: Patient B1 in 2006, now aged 58. She walks with a widened base with start hesitation and gait freezing and has impaired postural reflexes. She has to move her head in order to see the examiner's hand because of her cortical visual impairment. Finger tapping is within normal limits.

Video Segment 3: Patient A1 in 2001, aged 43. He is unable to hear the examiner's commands. He has bilateral dystonic posturing in the upper limbs, and an intermittent right upper limb dystonic tremor with the arms outstretched that becomes more persistent in the targeting nose position. ■

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