CASE REPORT

TOR1A mutation-related isolated childhood-onset generalised dystonia in South Africa

R van Coller,[1,2] MB ChB, MMed (Neurol), PhD; **C-M Schutte,**[1] MB ChB, MMed (Neurol), MD; **E Lubbe,**[1] MB ChB, FC Paed (SA), Cert Paediatric Neurology (SA); **B Ngele,**[1] MB ChB

[1] *Department of Neurology, School of Medicine, Faculty of Health Sciences, University of Pretoria, South Africa*
[2] *Pretoria Institute of Neurology, Die Wilgers, Pretoria, South Africa*

Corresponding author: *R van Coller (riaan.vancoller@up.ac.za)*

Background. Childhood-onset generalised dystonia is commonly caused by *TOR1A* mutations and is known to respond well to pallidal deep-brain stimulation (DBS) surgery. The incidence and prevalence of monogenic dystonia in individuals from Africa and specifically of African ancestry are unknown, and no local cases of *TOR1A* mutation dystonia are found in the literature.
Objectives. To describe our experience with the outcome of *TOR1A* mutation-positive patients with isolated generalised dystonia (IGD) of childhood onset who were treated with pallidal DBS.
Methods. All patients with *TOR1A* mutations from Steve Biko Academic Hospital and the Pretoria Neurology Institute in Pretoria, South Africa (SA), who underwent DBS for IGD of childhood onset were identified. We conducted a retrospective analysis of their demographics, clinical presentation and time to generalisation, genetic status and family history, and response to DBS treatment of the internal segment of the globus pallidus (GPi), utilising pre- and post-surgical scores of the United Dystonia Rating Scale (UDRS).
Results. Three patients, all of black African ancestry, were identified. The median age at onset was 12 years and the median time to surgery from dystonia generalisation was 3 years. Two children presented with cervical-onset dystonia. Two patients were related, representing the only two with a positive family history. All three patients had a positive outcome after surgery, with improvement of 67 - 90% on the UDRS recorded at last follow-up.
Conclusions. *TOR1A* mutations are found in SA patients of black African ancestry, with age of onset and generalisation comparable to those described in international studies. However, onset with cervical dystonia was more common than previously reported. Response to GPi DBS was excellent in all patients.

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Dystonia is a disabling movement disorder characterised by involuntary, sustained or intermittent muscle contractions, causing abnormal, repetitive movements, postures or both. Dystonic movements are often initiated or worsened by voluntary action (writing, walking and exercise) and associated with overflow muscle activation. Specific postures and additional features such as geste antagoniste and mirror movements may reflect its pathophysiology as a network disorder.[1] The estimated worldwide prevalence of dystonia is 7.6 - 16 per 100 000 in clinic-based epidemiological studies, with different prevalence figures reported in the various dystonia subtypes.[2] The diagnosis and management of dystonia have evolved significantly over the past decade, with more monogenic causes described and with deep-brain stimulation (DBS) surgery emerging as an effective option when drug therapy is not feasible or is ineffective.[3]

DYT-*TOR1A* is caused by a dominantly inherited mutation in *TOR1A* (chromosome 9q34). The common pathological mutation is a GAG deletion (C.907_909delGAG) causing loss of a single glutamic acid from torsin-A.[4] Patients from different ethnic backgrounds all carry the same mutation, indicating the possibility of an error during DNA replication caused by susceptible DNA structure. The gene product is torsin-1A, a member of the superfamily of ATPases. Torsin-1A is highly expressed in the substantia nigra, cerebellar Purkinje cells, thalamus, globus pallidus (GPi), hippocampus and cerebral cortex.[5] *TOR1A* mutations account for ~16 - 53% of early-onset dystonia in non-Ashkenazi Jewish persons.[6] Recently, rare missense mutations in *TOR1A* were also described.[7] The clinical presentation of *TOR1A* dystonia is heterogeneous, with a mean age of onset of 13 years (range 1 - 28 years) and low clinical penetration (30%).[6] The typical onset in early adolescence usually starts in one leg, often with movement-induced dystonia, with progression to the other leg and trunk, eventually causing generalised dystonia.[8]

Objectives

We provide what is to our knowledge the first report from Africa describing the presentation and successful management with DBS of children with *TOR1A*-related dystonia.

Methods

All patients from our units (Steve Biko Academic Hospital, Pretoria, and the Pretoria Neurology Institute, Die Wilgers, Pretoria) with childhood-onset generalised dystonia were identified in a retrospective study assessing patient-reported outcomes in DBS for dystonia. Patients who had the GAG deletion mutation in the *TOR1A* gene in their dystonia work-up were then included in the analysis. Genetic testing for the *TOR1A* mutation was done in the Division of Human Genetics, Faculty of Health Sciences, University of Cape Town.

A retrospective analysis of all patients' demographics, family history, clinical presentation, time to generalisation, time to DBS surgery and clinical outcome of DBS was performed using the

United Dystonia Rating Scale (UDRS) with assessments done before and at last follow-up after surgery.

The study was approved by the University of Pretoria Clinical Ethics Committee (ref. no. 36/2015). All patients or their legal guardians signed informed consent.

Results

Three patients were identified; the clinical data are summarised in Table 1. Two patients were female and one male, and all were of black African ancestry. The median age of dystonia onset was 12 years (range 9 - 12) and the median age at generalisation 14 years (range 10 - 17); the median time to surgery was 3 years (range 2 - 10). All three patients developed generalised dystonia affecting more than two limbs and trunk; two patients (patients 1 and 2) had cervical dystonia at the onset, while patient 3 had left-leg dystonia at the onset.

Genetic testing confirmed *TOR1A* mutations in all three affected individuals. DNA was extracted and exon 5 of the *TOR1A* gene located on chromosome 9q34 was analysed by polymerase chain reaction with confirmation with sequence analysis. Sequence variant c.904.c.906de1GAG was detected, confirming the diagnosis of *TOR1A* (DYT1) dystonia.

Patient 1

Cervical dystonia in this female patient started at the age of 12 years. Severe truncal dystonia then developed, making ambulation difficult. The work-up for secondary dystonia was negative and a 3-base pair (GAG) deletion on exon 5 was identified. The patient's symptoms were refractory to medical treatment, and DBS surgery was performed at the age of 15 years. The UDRS improved from 49 preoperatively to 15 at the last follow-up when the patient was 19 years old (Fig. 1).

Patient 2

Patients 2 (pedigree number IV:1) and 3 (pedigree number III:11) were related (Fig. 2). Patient 2 is a boy who developed cervical dystonia at the age of 9 years. Within 2 years, the dystonia rapidly progressed to involve his right arm, trunk and both legs. He was unable to feed himself or ambulate without aid, needing assistance with all activities of daily living. Magnetic resonance imaging of the brain was normal and standard investigations for childhood-onset dystonia did not reveal a secondary cause. The patient had a clear family history of dystonia: his mother was known to have segmental dystonia – cervical, oromandibular and laryngeal – and his grandfather had cervical dystonia. The family history revealed a large four-generation pedigree with many individuals affected with focal, segmental and generalised dystonia (Fig. 2). Initial treatment with botulinum toxin had been effective to manage the cervical component, but oral treatment with high-dose trihexyphenidyl was not effective. He was referred for DBS surgery of the internal segment of the GPi. Visual symptoms (phosphenes) developed after surgery, but disappeared when stimulation was changed to a more dorsal electrode contact. At follow-up 6 months after surgery, there was 90% improvement in the UDRS (49 to 5) (Fig. 1). Cervical dystonia improved markedly, with stabilisation of neck movements, and the patient was able to mobilise without support. Mild axial dystonia remained with abnormal posturing of his trunk, but all activities of self-care returned to normal.

Patient 3

Patient 3 developed paroxysmal episodes of dystonia, possibly induced by movement, at the age of 12 years. She eventually progressed to having left leg and truncal dystonia, which then spread further to involve the right leg and both arms. She was unresponsive to medical treatment and received DBS surgery at the age of 22 years, with the UDRS improving from 20 to 4.5 postoperatively (Fig, 1).

Discussion

To our knowledge, this is the first report of patients with *TOR1A* mutation-positive dystonia from Africa and in patients of African ancestry. It is important to document even the rarer genetic disorders from different ancestries throughout the world so as to alert clinicians to their existence, as information on the pathophysiology and new treatment options are becoming available at a rapid rate.

The three patients in our cohort were similar to the described Italian and French cohorts regarding age at onset and age at generalisation: median age at onset was 12 years in the SA patients v. 10.1 years in the Italian and 8.1 years in the French groups; median age at generalisation was 14 years in our patients and 13.5 years in the Italian group.[8,9] However, clinical presentation was distinctly different, probably reflecting the clinical heterogeneity that is well documented in *TOR1A* patients. Limb onset appears to be most prominent in other reports (93% of Italian patients), whereas in our cohort, cervical onset was more common (n=2/3). This mode of onset is especially important because patients with

Table 1. Clinical history and signs and UDRS before and after DBS surgery

						Areas affected at onset				Areas affected at generalisation				DBS			DBS adverse effects	
Patient no.	Gender	Current age (years)	Age at onset (years)	Age at generalisation (years)	Family history	Limb	Trunk	Cervical	Laryngeal	Limb	Trunk	Cervical	Laryngeal	Age at DBS (years)	UDRS before DBS	UDRS at follow-up	Improvement, %	Surgical	Stimulation induced
1	F	19	12	14	-	-	-	+	-	+	+	+	-	15	45	15	67	-	-
2	M	13	9	10	+	-	-	+	-	+	+	+	+	11	49	5	90	-	+*
3	F	23	12	17	+	+	-	-	-	+	+	-	-	22	20	4.5	78	-	-

UDRS = United Dystonia Rating Scale score; DBS = deep-brain stimulation; F = female; M = male.
*Patient 2 developed stimulation-induced visual disturbances with initial stimulation that resolved by changing the stimulation parameters.

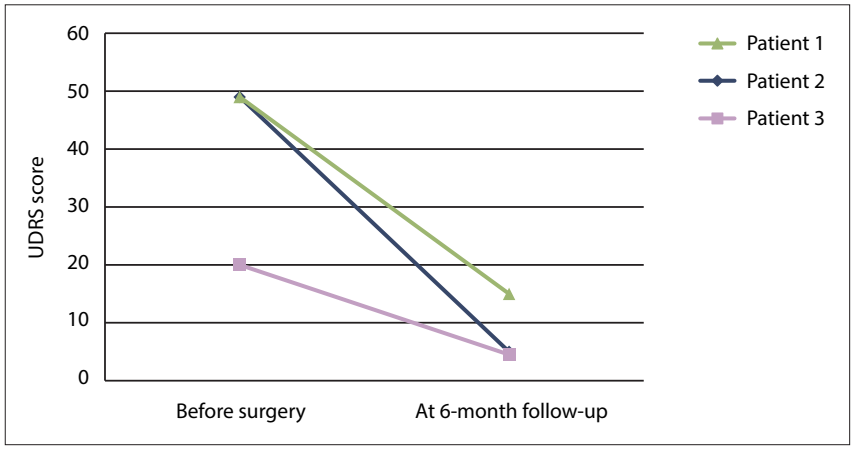

Fig. 1. Improvement of dystonia as illustrated by UDRS scores for the three patients before and after deep-brain stimulation surgery. (UDRS = United Dystonia Rating Scale.)

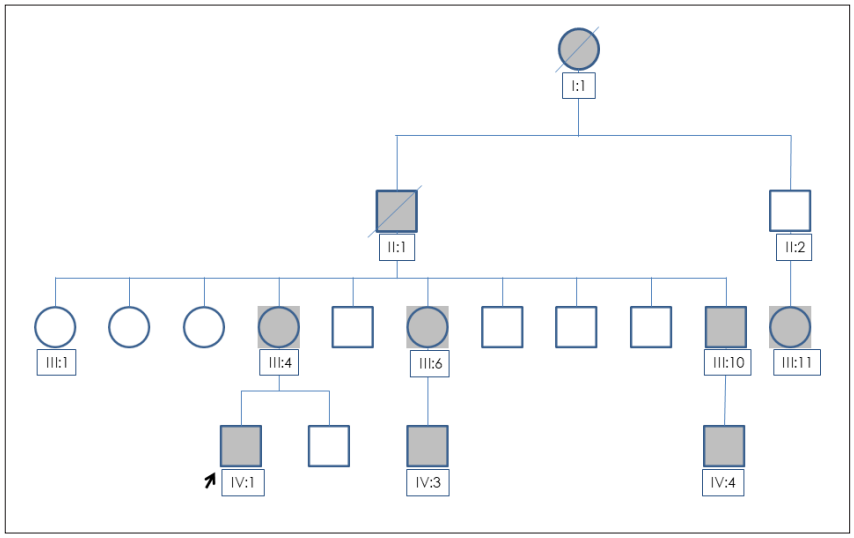

Fig. 2. Pedigree of family with isolated dystonia with prominent heterogeneity. Heterogeneity was noted among individuals and generations of this pedigree; there was an impression that later generations were affected at an earlier age and more severely. Notably, only individuals from generations III and IV progressed to generalised dystonia. Circles indicate females and blocks males, and affected individuals are shaded. The index case (IV:1, patient 2 in the article) is indicated with the arrow. Individual III:11 is patient 3 in the article.

other forms of generalised dystonia also commonly present with cervical and cranial onset, such as DYT-*THAP1* dystonia, which often does not respond as well to DBS as *TOR1A* dystonia.[8-10]

Patients 2 and 3 are part of a large four-generation family possibly with a relatively high penetrance of dystonia. Clinical heterogeneity is well described in families with *TOR1A* mutations, and it is remarkable in this family.[6] In our four-generation pedigree, affected individuals in each next generation had an earlier onset of dystonia symptoms than the previous generation, and the incidence of generalisation was clearly higher in the later generations. No explanation for this observation is evident at present, but the possibility of anticipation in single-mutation disorders explained by telomere shortening in studies with BRCA breast cancer has been raised.[11] Further study of epigenetic and gene regulatory mechanisms may lead to a better understanding of this unique finding.

All three patients in this cohort had an excellent and sustained response to pallidal DBS, with 67 - 90% improvement at longest follow-up, essentially changing them from individuals who required 24-hour support to young adults who could live independent and normal lives. These results compare well with the existing international data[9] and a meta-analysis on the outcome of all patients with generalised dystonia.[12,13]

Study limitations

A major limitation of our study is the small number of patients. The dataset is therefore too small to speculate on other reasons that may have contributed to an improved outcome (early surgery, orthopaedic complications, site of dystonia onset), but supports the published data that DBS is a clearly effective treatment for patients with *TOR1A* dystonia. Genetic testing in patients who present with childhood-onset dystonia is still not standard practice, and limited testing may have contributed to the small numbers of patients included. Low testing levels also impeded the interpretation of penetrance in the pedigree described here.

Conclusions

TOR1A mutations are found in SA patients of black African ancestry. Age at onset and progression compare with international cohorts, but the clinical phenotype shows differences, with cervical onset found more often in our cohort. As described in international publications, the response to GPi DBS was found to be excellent.

Declaration. None.

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Author contributions. All authors were involved in the discussion of the patients and contributed to the final manuscript. RvC identified and examined the patients and wrote the draft article, EL and BN contributed to patient follow-up and background research, C-MS co-wrote the article and provided critical revision, and all authors reviewed and approved the final manuscript.

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Conflicts of interest. None.

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