Parkinsonism and Related Disorders 68 (2019) 63–64

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Correspondence

A South African family with myoclonus-dystonia syndrome with a novel mutation in the SGCE gene responding to deep brain stimulation

ARTICLE INFO

Keywords:
Myoclonus-dystonia
SGCE-Gene mutation
DYT-SGCE
Deep brain stimulation

Myoclonus-dystonia syndrome (MDS), a childhood onset movement disorder, is characterised by axial and predominantly upper-body myoclonus with dystonia, and is often associated with disabling psychiatric symptoms [1]. Mutations in the epsilon-sarcoclygan gene (*SGCE, DYT-SGCE, DYT11*) is mostly described as the cause with additional methylation of the maternal carrying allele causing maternal imprinting; and subsequent expression of only the paternal allele [2]. Pharmacological treatment may be disappointing, although zonisamide may be efficacious (Level 1 evidence) and other drugs (valproate, levodopa, sodium oxybate) may be of benefit. Deep Brain Stimulation (DBS) of the Globus Pallidus interna and Ventral intermediate nucleus thalamus (Vim) is an alternative therapy with evidence in case studies and case-series showing efficacy and safety [3]. There are no published reports on South African patients with MDS. We identified a South African Afrikaner family with MDS and report on the findings of clinical and genetic studies performed on selected family members.

The index patient, a 40-year-old female (Fig. 1 (supplementary data), individual II-2), presented with severe treatment refractory axial myoclonus of the upper body, cranio-cervical dystonia and writer's cramp. The writer's cramp developed at the age of 12 and was followed by torticollis at 16 years old. Progressive myoclonus developed in the second decade of life. Action induced upper body myoclonus was prominent, triggered by walking, with impairment of activities of daily living. She had prominent anxiety, depressive mood and obsessive-compulsive disorder (OCD). The index patient's sister, a 43-year-old female (Fig. 1(supplementary data), individual II-1), had axial myoclonus from the age of 13; preceded by focal left leg dystonia and debilitating OCD. Patient II-I has two sons aged 20 and 17 (Fig. 1 (supplementary data)). The younger son (III-2) had been diagnosed with writer's cramp at the age of 8; without development of myoclonus or dystonia by 16 years old. At this stage it is uncertain whether he is affected. The older son (III-1) is treated for attention deficit disorder with co-morbid impulsivity and depressive mood. He has mild postural tremor. The father of the two affected sisters (Fig. 1 (supplementary data), individual I-1) had postural action induced arm myoclonus which was not disabling; and a history of depressive episodes.

Genetic screening of the family revealed a new variant in *SGCE*, a heterozygous c.824T > A substitution in exon 6 that leads to a premature stop codon in the protein at amino acid position 275 (p.L275X). All three affected individuals (I-1, II-1, II-2) as well as individual (III-2) are heterozygous carriers of p.L275X. This variant is absent from the ExAC database (http://exac.broadinstitute.org/) and, to our knowledge, has not previously been reported. The frequency of p.L275X was screened in 246 ethnically-matched controls and was not found. Additional support for the pathogenicity of this variant is provided by *in silico* prediction software Mutation-Taster (http://www.mutationtaster.org) that predicted the variant to be “disease-causing”. Furthermore, the leucine residue at position 275 is evolutionarily-conserved and the mutation was predicted to have a very high impact with a Combined Annotation Dependent Depletion (CADD) score of 43 (Variant Effect Predictor, VEP; http://www.ensembl.org/Homo_sapiens/Tools/VEP).

DBS surgery was done in patient II-1 and II-2 targeting the posteroventral segment of the GPi. Videos of the patients showing them before, and four years after surgery are shown in the supplementary video segments 1 and 2. These were assessed by a blinded rater (JC). Significant improvement was observed at initial follow up six weeks after surgery and was sustained at four year follow up. Outcomes were gratifying with improvements in dystonia (Unified Dystonia Rating Scale) of 47% (II-1) and 66% (II-2), and improvement of myoclonus (Unified Myoclonus Rating Scale) of 58% (II-2) four years after surgery (Table 1). Regarding psychiatric symptoms, there was a significant improvement in OCD and moderate improvement of anxiety and depression in both individuals (Table 1). Both patients remained on stable stimulation settings for the entire follow-up period stimulating the two deepest contacts with moderate-high pulse width (120 - 180 μs) and standard frequency (130Hz). No surgical or stimulation-induced side-effects were reported.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.10.001.

Pre- and post DBS videos of individual II-1 (video 2) and II-2 (video 1). In both videos segment 1 shows myoclonus and dystonia before DBS surgery and segment 2 at last follow up, 4 years after surgery. In both videos head and cervical myoclonus is prominent (oscillatory myoclonus) and is completely suppressed after DBS.

Here, we report on an African Afrikaner family with a novel mutation in the *SGCE* gene causing MDS with long-term improvement of motor and obsessive-compulsive symptoms with DBS of the posteroventral GPi. These findings are in keeping with previous reports with

https://doi.org/10.1016/j.parkreldis.2019.10.001
Received 23 July 2019; Received in revised form 17 September 2019; Accepted 2 October 2019

Table 1
Summary of clinical outcomes before and after GPi Deep Brain Stimulation surgery.

Patient	Sex	Age at onset	Age at surgery	UMRS			UDRS			HADS			Y-BOCS			DBS Settings at last follow up[a]	
				B	M	Y	B	M	Y	B	M	Y	B	M	Y	Left GPi	Right GPI
II-2 [b]	F	12	33	69	33	ND	29.5	ND	15.5	15	13	13	ND			3.5V/120 μs	3.5V/120 μs
II-1	F	6	37	ND	28	ND	43	ND	14.5	34	8	8	36	3	5	3.2V/180 μs	3.0V/180 μs

Abbreviations: F: female; B: Score before surgery; M: Score six months after surgery; Y: Score at last follow up after surgery at 4 years; UMRS: United Myoclonus Rating Scale; UDRS: United Dystonia Rating Scale; HADS: Hospital Anxiety and Depression Scale; Y-BOCS: Yale Obsessive Compulsive Scale; ND: Not done.

[a] Both sides were programmed in monopolar with most ventral contact as the anode and case as the cathode. (0-/C+ and 8-/C+). Frequency in both cases set at 130Hz.

[b] Index case.

long-term follow up of GPi DBS in MDS [4]. Although previous reports indicated worsening of some psychiatric features [5], an improvement in social adjustment was reported, reflecting improved psycho-social skills, at longer than 5 years in a French cohort [4]. Multiple factors, including social support, genetic mutations and specific psychiatric diagnosis might play an important prognostic role in the outcome of psychiatric symptoms after surgery. We hypothesise that certain pre-surgical psychiatric co-morbidity, like OCD, might respond well to DBS and warrant further study. The outcome of DBS treatment in these patients support surgery as an early treatment option, contributes to the sparse data available on genetic causes and treatment options in MDS and argues for the establishment of an international register of pooled genetic and outcome data on MDS.

Funding sources

This work was supported by Medtronic South Africa, the National Research Foundation of South Africa (Grant Number: 106052) and the South African Medical Research Council (Self-Initiated Research Grant). We acknowledge the support of the NRF-DST Centre of Excellence for Biomedical Tuberculosis Research; South African Medical Research Council Centre for Tuberculosis Research; Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town.

Documentation of authors' roles

RvC and CS conceptualized the study. RvC was responsible for accumulation of data and write up of the manuscript, SB and AN were responsible for the genetic analysis and assisted with write up of the manuscript, JC performed blinded clinical assessments and provided advice on the manuscript and CS supervised the data accumulation and interpretation and was involved in the write up of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

Ethics statement

The study was approved by the Clinical Ethics Committee University of Pretoria, number 36/2015. All patients signed written informed consent to participate in the study. Additional written consent was obtained from individual II-1 and II-2 for the online publication and dissemination of the video material; and is on file.

The authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Declaration of competing interest

RvC received honoraria for teaching from Medtronic and CiplaMedpro.

Acknowledgements

We thank the family for taking part in the study. We also wish to thank the Western Province Blood Transfusion Service for providing the controls for the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.10.001.

References

[1] E. Roze, A.E. Lang, M. Vidailhet, Myoclonus-dystonia: classification, phenomenology, pathogenesis, and treatment, Curr. Opin. Neurol. 31 (2018) 484–490, https://doi.org/10.1097/WCO.0000000000000577.

[2] L. Rachad, N. El Kadmiri, I. Slassi, H. El Otmani, S. Nadifi, Genetic aspects of myoclonus–dystonia syndrome (MDS), Mol. Neurobiol. 54 (2017) 939–942, https://doi.org/10.1007/s12035-016-9712-x.

[3] K.M. Smith, M. a Spindler, Uncommon Applications of Deep Brain Stimulation in Hyperkinetic Movement Disorders, Tremor and Other Hyperkinetic Movements, (2014), pp. 1–17, https://doi.org/10.7916/D84X56HP.

[4] Z. Kosutzka, S. Tisch, C. Bonnet, M. Ruiz, E. Hainque, M.L. Welter, F. Viallet, C. Karachi, S. Navarro, M. Jahanshahi, S. Rivaud-Pechoux, D. Grabli, E. Roze, M. Vidailhet, Long-term GPi-DBS improves motor features in myoclonus-dystonia and enhances social adjustment, Mov. Disord. (2018) 1–8, https://doi.org/10.1002/mds.27474.

[5] M.F. Contarino, E.M. Foncke, D.C. Cath, P.R. Schuurman, J.D. Speelman, M.A.J. Tijssen, Effect of pallidal Deep Brain stimulation on psychiatric symptoms in myoclonus-dystonia due to epsilon-sarcoglycan mutations n, Arch. Neurol. 68 (2011) 1087–1088, https://doi.org/10.1001/archneurol.2010.322.

Riaan van Coller*
Department of Neurology, University of Pretoria, Pretoria, South Africa
E-mail address: rvcoller@gmail.com.

Soraya Bardien, Annika Neethling
Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

Jonathan Carr
Division of Neurology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

Clara Schutte
Department of Neurology, University of Pretoria, Pretoria, South Africa

* Corresponding author. Department of Neurology, University of Pretoria, Pretoria, South Africa.