A Case Control Series of Thalamic DBS in Patients with Demyelinating Neuropathy and Medication Refractory Tremors

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BACKGROUND

- Essential tremor (ET) is one of the most common movement disorders and up to 55% of tremors are refractory to standard pharmacotherapy.
- Deep brain stimulation (DBS) to the ventral intermediate nucleus (ViM) nucleus can be an effective treatment[1] for refractory ET.
- 13-40% of patients with ViM DBS are reported to develop tolerance to continuous stimulation, but the reasons are not understood[2]
- Observed phenomena of tolerance include:
  - Tremor rebound: a temporary increase in tremor intensity over the pre-operative state after switching off DBS[3]
  - Habituation: a loss of sustained tremor control over a short duration of follow-up[4]
  - Late therapy failure: loss of tremor control up to 1 year after stable tremor control with DBS.
- We have recognized a group of patients with medication refractory tremors (MRT) and co-morbid demyelinating peripheral neuropathy (PN) in whom we have had difficulty achieving sustained long term tremor control due to accelerated tolerance.
- We aim to describe the long term management of ViM DBS patients with MRT-PN compared to those with uncomplicated ET

METHODS

- Patients with MRT-PN were identified through our clinical practice and DBS database.
- A control group was established from a database search of patients implanted with ViM DBS from 2003-2006 at the PDCMDC (n=50)
  - *Inclusion criteria*: >10 years of diagnosed ET with at least 1 family member affected and 4 continuous implant years of follow-up
  - *Exclusion criteria*: Other etiologies of tremor, evidence of PN on exam, diabetes or other conditions associated with PN, and possible parkinsonism.
- A retrospective chart review was conducted to record patient demographics, frequency of programming visits, degree of amplitude adjustments and symptoms of tolerance; data obtained was analyzed using descriptive statistics.

MRT-PN CASE HISTORIES

Patient 1*: 77 y/o with bilateral moderate to severe postural & kinetic tremor with history of restless legs syndrome (RLS) and hypothyroidism incidentally found to have PN on exam. After undergoing bilateral DBS he noted robust improvement after each programming session, effects wore off after 2-3 days. He had frequent visits due to habituation and could not tolerate DBS off due to severe tremor rebound.*

Patient 2: *64y/o with tremors "his whole life" underwent R ViM DBS and insufficient tremor control and side effects for which he was referred to our clinic. He had marked large amplitude proximal tremor in the left arm and moderate postural tremor in the right, frequent visits due to habituation and could not tolerate DBS off due to severe tremor rebound. After lead revision his DBS was off for 3 weeks; during this time his tremors improved to their pre-op state.*

Patient 3: *70y/o with moderate to severe postural and kinetic tremors in the left hand with history of RLS and cervical stenosis underwent R ViM DBS. He was lost to follow-up for 22 months and returned to our care in 2006 with a new L ViM DBS where he was noted to have frequent visits due to habituation.*

Patient 4: *53y/o with a 15-year history of minimal tremors in R hand and acute worsening 3-6 months prior to presentation when he was diagnosed with CIDP. He underwent bilateral DBS for moderate to severe activity dependent tremors with mild postural and kinetic tremors. He noted robust improvement of tremors for 1-2 days after each programming session. He had frequent visits due to habituation and could not tolerate DBS off due to severe tremor rebound.*

Patient 5: *74y/o with new onset mild to moderate bilateral lateral postural tremors 2 years prior to evaluation underwent DBS for neuropathic tremors. He noted robust tremor improvement for 2-3 days after each programming session. He had frequent visits due to habituation and could not tolerate DBS off due to severe tremor rebound.*

RESULTS

Table 1: MRT-PN Group Demographics

	Age eval	G	H	Dx & tremor Duration	FH	dPN diagnosis	Evaluation of dPN	Impl years	Year of last visit	Impl Site (year)	Device
#P1	77	M	R	ET >20year	Y	dPN (NOS) 2001	EMG 2007: mild proximal demyelinating peripheral neuropathy	9.92	2011*	L ViM (2001) R ViM (2004)	Soletra
#P2	64	M	L	ET >20yr	Y	CIDP (1995)	Dx OSH Appropriate response to IVIG and steroid therapy	0.58	2010	R ViM (OSH 2005)	Soletra
#P3	70	M	L	ET (L>20yrs, R 2yrs)	Y	MMN (1995)	EMG 2007: Multifocal demyelinating motor and sensory neuropathy. SPEP: Lambda spike. Symptoms stable on mycophenalate	4.44	2009	R ViM (2002) L ViM (OSH 2005)	Soletra
#P4	53	M	R	Possible ET >15 yrs	N	CIDP (2008)	EMG 2008: sensorimotor polyneuropathy CSF protein 81, cell 1. Appropriate response plasmapheresis & mycophenolate	3.7	2011*	R ViM (2009) L ViM (2009)	Soletra
#P5	74	M	R	Neuropathic tremor 2yr hx	Y	IgM dPN (1997)	EMG 1997: distal sensorimotor polyneuropathy. Sural nerve bx 2005: severe demyelinating/remyelinating neuropathy. CSF protein 75 cell 0. Unclear response plasmapheresis	4.64	2010	R ViM (2005) L ViM (2005)	Soletra

Eval= at evaluation; G= Gender; H= Handedness; Dx= diagnosis, yr= year; hx= history; FH= Family history; Y= yes; N= no; Impl= implant; R= right; L= left; ET= Essential tremor; dPN= demyelinating peripheral neuropathy; MMN= multifocal demyelinating motor and sensory neuropathy; CIDP= chronic idiopathic demyelinating polyneuropathy; EMG= Electromyography and nerve conduction; bx= biopsy; CSF= cerebrospinal fluid; *= actively followed; ViM= ventral intermediate nucleus of the thalamus; OSH= outside facility

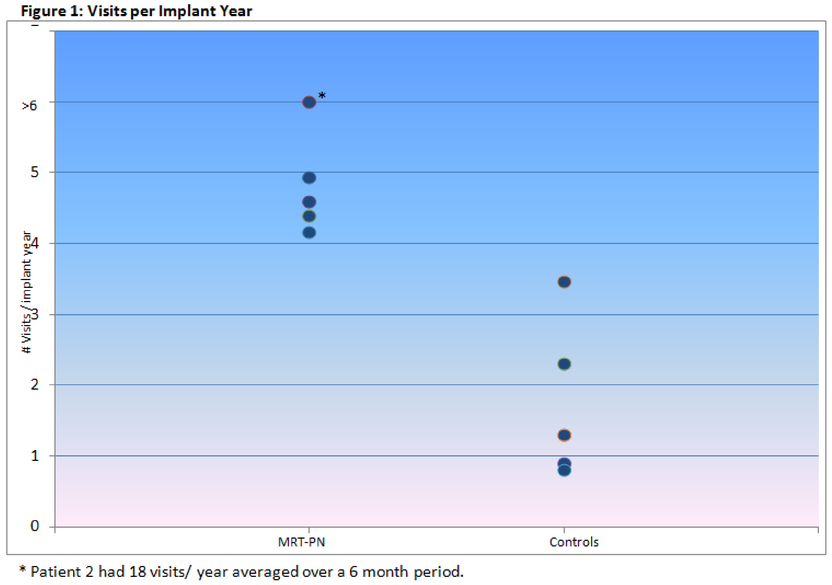
Table 2: Control Group Demographics

	Age eval	G	H	Dx & tremor Duration	FH	Co-morbidities	Impl years	Date last visit	Impl Site (year)	Device
#C1	75	M	R	ET >20yr R>L	Y	None	5.75	2011*	R ViM (2006) L ViM (2006)	Soletra
#C2	70	M	R	ET >15 yrs	Y	None	5.17	2011*	R ViM (2006) L ViM (2006)	Soletra
#C3	53	M	R	ET >20yrs	Y	Bipolar disorder†	4.58	2010	L ViM (2006)	Soletra
#C4	64	F	R	ET >20 yrs	Y	None	6.42	2011*	R ViM (2005) L ViM (2006)	Soletra
#C5	44	F	R	ET >20 yrs	Y	None	5.83	2009	R ViM (2003) L ViM (2003)	Soletra
#C6	74	M	R	ET >20 yrs	Y	None	6.17	2009	L ViM (2003)	Soletra
#C7	67	M	U	ET >20 yrs	Y	None	6.92	2011*	L ViM (2004)	Soletra

Eval= at evaluation; G= Gender; H= Handedness; Dx= diagnosis, FH= Family history; Y= yes; N= no; Impl= implant; R= right; L= left; ET= Essential tremor; *= actively followed; ViM= ventral intermediate nucleus of the thalamus; †treated with lithium for 15 years

- C3 had tremor onset years prior to initiating Lithium. He has remained on stable doses for several years prior to implantation.

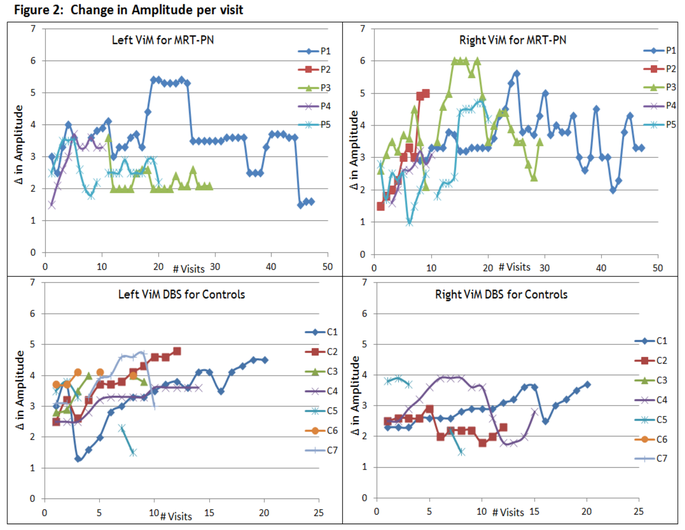
Figure 1: Visits per Implant Year



* Patient 2 had 18 visits/ year averaged over a 6 month period.

RESULTS (continued…)

Figure 2: Change in Amplitude per visit



- All patients in the MRT-PN group noted improvement of tremors with any Δ in amplitude
- A cycling of amplitude over time was observed

DISCUSSION

- All patients in the MRT-PN group developed tremor habituation and severe rebound to continuous DBS resulting in suboptimal long term tremor control while the uncomplicated ET group did not.
- A few case reports have suggested successful short term (6-9mos) suppression of neuropathic tremors in subjects with severe acquired autoimmune or genetic demyelinating PN[5-9].
- The diagnosis of ET in patients with PN, particularly demyelinating subtypes, which are often associated with phenomenologically identical tremors, may be difficult[10]. It is possible that our MRT-PN patients have co-morbid neuropathic tremors.
- Neuropathic tremors are theorized to be secondary to abnormal cerebellar processing of distorted muscle spindle input due to slowed peripheral conduction. Altered sensory feedback due to deafferentation may underlie the tremor pathophysiology and abnormal response to ViM DBS[11].
- We suggest that the presence of demyelinating PN is a risk factor for suboptimal tremor control due to high risk of tolerance and is a relative contraindication to continuous stimulation to the ViM nucleus.
- The observation of short term tremor suppression with parameter adjustment suggests DBS may still be an option for treatment of patients with debilitating MRT associated with PN or neuropathic tremors. Future studies should be directed at alternate targets and/or new methods of stimulation delivery.

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