Habituation and Rebound to Thalamic DBS in Long-Term Management of Tremor Associated with Demyelinating Sensorimotor Peripheral Neuropathy

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BACKGROUND

- 13-40% of patients with ViM DBS for essential tremor (ET) are reported to develop tolerance to continuous stimulation, for unclear reasons[1]
- Observed phenomena of tolerance include:
  - Tremor rebound: a temporary increase in tremor intensity over the pre-operative state after switching off DBS[2]
  - Habituation: a loss of sustained tremor control over a short duration of follow-up[3]
  - Late therapy failure: loss of tremor control up to 1 year after stable tremor control with DBS[1].
- Disputed theories for tolerance include:
  - Natural disease progression
  - Inadequate electrode location
  - Resolution of microthalamotomy effects
  - Adaption of neural networks to localized chronic stimulation[3].
- We observed that patients with demyelinating sensorimotor peripheral neuropathy (PN) treated by ViM DBS experienced worse outcomes with tolerance.
- We aim to describe the long term management of ViM DBS patients with medication refractory tremor associated with PN (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: *88 y/o LHM with bilateral moderate to severe postural & kinetic tremor for more than 10 years. Left ViM DBS placed in 2001 and right ViM in 2004 yielded a good response. By 2007, he reported loss of benefit of adjustments after 1 week. Re-programming typically resulted in immediate near-complete control of tremors that would wear off 2-3 days later. He was unable to tolerate DBS off due to severe tremor rebound. (Video1)*

Patient 2: *66y/o LHM underwent right ViM DBS in 2010 at an outside institution. He had substantial improvement in tremor for 2 weeks followed by rapid loss of re-programming effects within 24 hours despite bi-weekly adjustments. Tremors markedly worsened from their pre-operative baseline with DBS off. 16 days "off stimulation", tremors gradually returned to pre-operative baseline severity.*

Patient 3: *81y/o LHM with 20 year history of left hand and 2 year history of right hand tremors. Right ViM was placed in 2002 with excellent control of tremors. By 2003 the effects of stimulator adjustments only lasted a few days. Eventual left ViM DBS placed at an outside institution yielded good control of right hand tremors. He required frequent reprogramming visits for left hand tremor control, now with prominent proximal component. He was unable to tolerate DBS off" due to tremor rebound.*

Patient 4: *57y/o RHM with 10-15 year history of minimal right arm tremors that worsened over 3-6 months while developing neuropathy. In 2009 staged bilateral ViM DBS yielded good tremor control. Re-programming was requested to address persistent impaired ADLs lasting for about 1 week. In 2011, "off" stimulation examination showed marked tremor rebound with bilateral 4+ rest, and need for assistance to stand and ambulate. He was unable to tolerate turning off the stimulator for prolonged periods. (Video 2)*

Patient 5: *84y/o RHM with bilateral tremors for more than 10 years. Bilateral ViM DBS, yielded marked improvement. By 2009, he developed loss of programming effects after several days, and intolerable left arm tremor with stimulator "off". Marked asymmetric tremor rebound "off" stimulation occurred which he could not tolerate stimulator "off" for any length of time.*

RESULTS

Table 1: Clinical Characteristics of Patients with MRT-PN

	Age	G	H	PN diagnosis (year)	Evaluation of PN	Tremor duration pre-DBS	FH	Implant Site (year)	Implant years
P1	88	M	R	PN (NOS) 2001	-EMG 2007: mild proximal demyelinating peripheral neuropathy	>20year	Y	L ViM (2001) R ViM (2004)	9.92
P2	66	M	L	CIDP (1995)	-Neuropathy work-up unavailable -Appropriate response to IVIG and steroids	>20yr	Y	R ViM (2005)	0.58
P3	81	M	L	MMN (1995)	- EMG 2007: Multifocal demyelinating motor and sensory neuropathy. - SPEP: Lambda spike, anti-MAG 204,000. - Treated with IVIG, plasmapheresis, cyclophosphamide and rituximab with stabilization of symptoms.	L>20yrs, R 2yrs	Y	R ViM (2002) L ViM (2005)	4.44
P4	57	M	R	CIDP (2008)	- EMG 2008: sensorimotor polyneuropathy - CSF protein 81, cell 1. - Appropriate response to plasmapheresis & mycophenolate	>15 yrs	N	R ViM (2009) L ViM (2009)	3.7
P5	82	M	R	IgM PN (1997)	- EMG 1997: distal sensorimotor polyneuropathy. - Sural nerve bx 2005: severe demyelinating/remyelinating neuropathy. - CSF protein 75 cell 0. - Unclear response to plasmapheresis	2yr	Y	R ViM (2005) L ViM (2005)	4.64

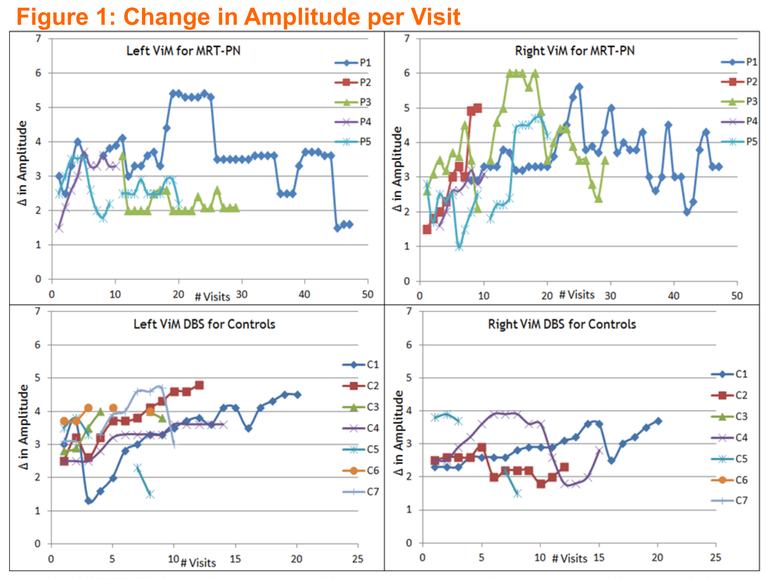
G= Gender; H= Handedness; Y= yes; N= no; R= right; L= left; MMN= multifocal demyelinating motor and sensory neuropathy; CIDP= chronic idiopathic demyelinating polyneuropathy; EMG= Electromyography and nerve conduction; bx= biopsy; CSF= cerebrospinal fluid; ViM= ventral intermediate nucleus of the thalamus.

Table 2: Clinical Characteristics of patients with ET without clinically evident neuropathy

	Age	G	H	Tremor Duration pre-DBS	FH	Implant Site (year)	Implant years
C1	82	M	R	20yr R>L	Y	R ViM (2006) L ViM (2006)	5.75
C2	78	M	R	>15 yrs	Y	R ViM (2006) L ViM (2006)	5.17
C3	66	M	R	>20yrs	Y	L ViM (2006)	4.58
C4	72	F	R	>20 yrs	Y	R ViM (2005) L ViM (2006)	6.42
C5	54	F	R	>20 yrs	Y	R ViM (2003) L ViM (2003)	5.83
C6	84	M	R	>20 yrs	Y	L ViM (2003)	6.17
C7	76	M	U	>20 yrs	Y	L ViM (2004)	6.92

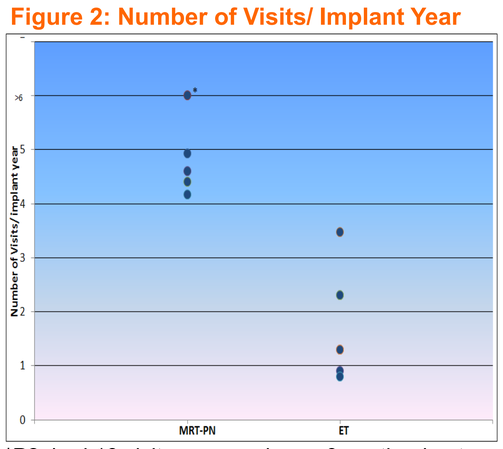
G= Gender; H= Handedness; Dx= diagnosis, FH= Family history of tremor; Y= yes; N= no; R= right; L= left; ET= Essential tremor; ViM= ventral intermediate nucleus of the thalamus.

Figure 1: Change in Amplitude per Visit



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

Figure 2: Number of Visits/ Implant Year



*P2 had 18 visits averaged over 6months due to suboptimal tremor control.

Video 1: Tremor habituation. In 1st segment, P1's is shown 3 months after last programming session where settings were optimized. He reported tremors worsened within 1 week adjustment. In 2nd segment, a minor reduction in pulse width (15μs) and frequency (15Hz) to right ViM and 0.1V increase to left ViM resulted in marked improvement of rest, postural and kinetic components of his tremors. In 3rd segment, bilateral DBS has been turned "off" for 30 minutes, with marked worsening of tremors consistent with tremor rebound.

Video 2: Tremor rebound. In the 1st segment, P4 is shown at baseline, before DBS. The 2nd segment shows P4 after 37 months of continuous stimulation. The 3rd segment is with bilateral DBS "off" for 5 minutes. The patient experiences tremor that is significantly worse compared to his pre-operative state, consistent with rebound.

DISCUSSION

- 5/5 MRT-PN cases developed tremor habituation and severe rebound to continuous DBS vs. 0/7 in the control group.
- Typical ET progression is unlikely to explain symptoms.
- Previous case reports have described short-term (6-12mo) tremor suppression with ViM DBS in patients with tremor and various acquired autoimmune and genetic demyelinating neuropathies.[4-10] Our series differs because all of our MRT-PN patients likely had ET, and were followed for a longer period of time.
- DBS may reduce tremor severity in ET by masking burst-driver inputs to the thalamus via the cerebellum,[10] suggesting that tremor habituation in ET results from resetting the oscillatory frequency of thalamic neurons.[11]
- A cycling of settings was transiently beneficial in MRT-PN, suggesting that central oscillators are only temporarily "re-set".[13,14]
- Tolerance is likely a stimulation-induced phenomenon and the presence of demyelinating PN in our MRT-ON increases the risk for tolerance; MRT-PN may represent a relative contraindication to ViM DBS.
- Limitations include: lack of detailed homogenous tremor assessments due to retrospective study, lack of formal neuropathy evaluations on all patients and MRI was not performed systematically. We did not include all patients with habituation or rebound, therefore it is possible that other factors not identified may contribute to tolerance.
- Alternate targets such as the subthalamic area,[12,13] should be explored in patients similar to ours with MRT-PN. Temporally irregular stimulation,[12,14] as opposed to continuous stimulation, or even closed-loop systems based on brain sensing[15] may also show promise with respect to addressing risk of tolerance.

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