



Sensory abnormalities in unaffected relatives in familial adult-onset dystonia

Abstract—Somatosensory abnormalities are found in adult-onset primary torsion dystonia (PTD). Therefore we assessed spatial discrimination thresholds (SDT), a measure of spatial acuity, in four multiplex families with adult-onset PTD. In family members aged 20 to 45 years vs controls (mean + 2.5 SD), abnormal SDTs were found in four of five affected with adult-onset PTD and in 12 of 49 unaffected relatives. Sensory abnormalities may be an endophenotype, possibly expressed later as adult-onset PTD.

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The etiology of adult-onset primary torsion dystonia (PTD) remains largely unknown. Studies of adult-onset PTD families indicate an autosomal dominant inheritance with reduced penetrance of 12% to 15%.^{1,2} The identification of the genetic causation of adult-onset PTD has been difficult because informative families are rare due to the low penetrance of the phenotype and the absence of a structural or biochemical marker.

However, there are somatosensory deficits in dystonia, which may have a primary role in the pathogenesis of dystonia.³ A number of sensory abnormalities have been identified in adult-onset PTD including sensory discrimination.⁴⁻⁷

The spatial discrimination threshold (SDT) is a measure of spatial acuity and is impaired bilaterally in focal hand dystonia (FHD) and cervical dystonia.^{5,6} If sensory abnormalities are primary, they may be presymptomatic markers (i.e., an endophenotype). This is a subclinical trait associated with the expression of an illness and represents the genetic liability to the disorder among unaffected subjects. We postulated that there might be abnormal SDTs in asymptomatic relatives in familial adult-onset PTD.

Methods. *Subjects.* The 106 control subjects were healthy volunteers aged ≥ 20 years. Screening excluded subjects with any neurologic abnormality, palmar callouses, or extended use of vibrating tools.

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The study subjects were from four multiplex adult-onset PTD Irish families. The four probands had cervical dystonia and other family members were examined for the presence of dystonia.⁸ Videotaped examinations were reviewed by at least two neurologists experienced in the assessment of dystonia (MH, TL, SB, RSP). Consensus as to the presence of dystonia and the clinical phenotype was made.

SDT testing of family members was performed by an author blinded to the agreed status (JO'D). In all, 114 members from the four families were assessed by video; 17 family members were rated as being affected by adult-onset PTD.

SDT testing showed a ceiling effect in control subjects ≥ 45 years. Therefore, only family members aged < 45 years were examined. In this age group, there were 66 family members, but only 54 were eligible and consented to examination. Five subjects affected by adult-onset PTD and 49 unaffected relatives were examined including 11 siblings, 13 children, and 25 second-degree relatives. Ethical approval was granted by the Ethics Committee, St. Vincent's University Hospital.

Sensory testing. Spatial discrimination was tested using JVP domes (Stoelting Co, IL). These are eight plastic domes with gratings of widths 0.35 mm to 3.0 mm. The SDT was determined using the subject's index finger distal fat pad. Subjects were seated at a comfortable height opposite the examiner, separated by an opaque textile screen on a table. The index finger was held extended with the nail opposed against the table. Beginning with the largest width grating and proceeding through gradually narrower ones, domes were applied for 1 to 2 seconds with enough pressure to indent the skin 1 mm. Twenty applications of each dome in a predetermined random orthogonal direction were made until less than 60% were correct. The subject was required to answer with a force-choice paradigm immediately, receiving no feedback. The SDT for each hand was calculated by linear interpolation of the 75% level. The SDT for each individual was calculated as the mean of both index fingers.

Statistics. Because of the ceiling effect, the control subjects were divided into two groups: group 1 was 20 to 45 years of age and group 2 was ≥ 45 years of age. The upper limit of normal SDT for group 1 was determined as the mean SDT of the 20- to 45-year-old group plus 2.5 SD. Any SDT in family members greater than this value was considered abnormal. The Mann-Whitney test was used to compare median values of groups of relatives to the control subjects' median using Prism 4 (GraphPad, CA).

Results. There were 106 control subjects (aged 38.3 ± 14.1 , range 20 to 78 years). In group 1 ($n = 70$), the average age was 29.5 ± 6.1 years and the mean SDT (\pm SD) was $1.157 \text{ mm} (\pm 0.328)$. The upper limit of the normal SDT was therefore 1.977 mm (mean + 2.5 SD). No control SDT was greater than this. In group 2, age (\pm SD) was 55.6 ± 7.9 years and the mean SDT (\pm SD) was 2.119 mm

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Table Summary of total number of individuals in each of the four pedigrees and the number who have adult-onset primary torsion dystonia

Pedigrees examined	Ped 005	Ped 006	Ped 008	Ped 010	Total
Total no. in family	32	26	41	15	114
Total affected by PTD	4	3	6	4	17
Number in family aged 20–45 years	12	19	26	9	66
Affected by PTD, aged 20–45 years	0	1	3	1	5
Affected by PTD, abnormal SDT	0	1	2	1	4
Unaffected children with abnormal SDT (total children examined)	1 (3)	0 (0)	1 (3)	4 (7)	6 (13)
Unaffected siblings with abnormal SDT (total siblings examined)	0 (0)	0 (5)	1 (6)	0 (0)	1 (11)
Unaffected 2nd deg relatives with abnormal SDT (total examined)	1 (2)	1 (9)	3 (14)	0 (0)	5 (25)
Total abnormal SDT results (number examined by SDT)	2 (5)	2 (15)	7 (26)	5 (8)	16 (54)

The fourth row indicates the number of family members aged 20–45 years. The rows below summarize the number of affected family members and relatives having abnormal SDT findings with, in brackets, the numbers examined in each group.

PTD = primary torsion dystonia; SDT = spatial discrimination threshold.

(± 0.621). The ceiling effect precluded the calculation of an upper limit.

Sixteen of the 54 family members examined (aged 20 to 45 years) had an abnormal SDT. Four of five subjects affected with adult-onset PTD and 12 of 49 unaffected family members were outside the normal limit (table, figure). Four of the five family members affected with adult-onset PTD had a mean SDT greater than the normal limit (1.977 mm), and the median SDT (2.292 mm) was different from the median of the control group (1.075 mm, $p = 0.0004$). Six of 13 children had an abnormal SDT, with a group median SDT of 1.850 mm ($p < 0.0001$). One of the eleven siblings had an abnormal SDT. Their group median was 1.442 mm ($p = 0.0015$). Five of 25 second-degree relatives

had abnormal SDTs. This group showed a trend toward a difference ($p = 0.0667$). The comparison of variance was significant (Kruskal-Wallis statistic = 37.86, $p < 0.0001$).

Discussion. This study has shown that in multiplex adult-onset PTD families, one can demonstrate SDT abnormalities in at-risk members who have no dystonia. It may be postulated that the sensory abnormality, a structural or physiologic cerebral abnormality, represents an endophenotype. It may or may not be expressed later as adult-onset PTD, possibly dependent upon modifying genetic or environmental factors. Previous studies of SDT in adult-onset PTD have compared small numbers using means or Kaplan-Meier statistics.^{4,5} In this study, we have defined an abnormal SDT as a value greater than 2.5 SD above the mean of a large control population in order to identify individual family members with an abnormal SDT. Due to the age effect, abnormal SDTs were only determined in younger adults.

Voxel-based morphometry has shown bilaterally increased volume of the primary somatosensory cortices (S1) in 36 patients with unilateral FHD.⁷ The authors suggest that bilateral anatomic changes in S1 may be primary. Bilateral abnormalities in S1 in patients with unilateral FHD were also found by magnetoencephalography, suggesting this might be an endophenotype.⁶ The endophenotype concept has been demonstrated with *DYT1*. In a transcranial magnetic stimulation study of manifesting and non-manifesting *DYT1* mutation carriers, both groups showed similar abnormalities consisting of impaired intracortical inhibition and shortened silent period.⁹ Similarly, group differences have been demonstrated in *DYT1* using PET.¹⁰

A problem with JVP domes is the age-related decrease in sensitivity seen in the control subjects over age 45 years. The ceiling effect is due to age-related changes in the peripheral nervous system, particularly the density of slowly-adapting type 1 fibers.

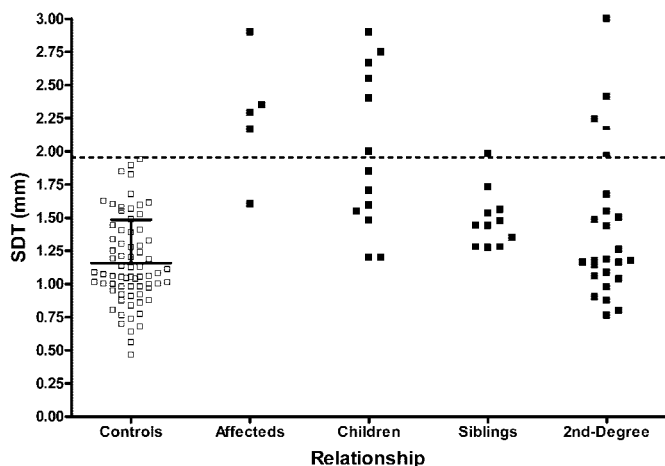


Figure. Scatter plot of spatial discrimination thresholds (SDT) for the control subjects, affected family members, and relatives of affected family members grouped by closest relationship to an affected family member. All subjects were 20 to 45 years of age. The horizontal dotted line represents the mean SDT of control subjects plus 2.5 SD. Abnormal SDT ($> \text{mean} + 2.5 \text{ SD}$ of control subjects) were found in four of five affected family members, six of 13 children, one of eleven siblings and five of 25 second-degree relatives.

Their receptors, Merkel cells, are capable of 0.5 mm spatial resolution and are responsible for form and texture discrimination. In the commercial set of JVP domes, the largest grating is 3 mm. Because the mean age at onset of cervical dystonia is 41 years, further studies using larger gratings in older subjects are required.

If these results are replicated, SDTs might be a useful biologic marker of gene carriage in adult-onset PTD. Not all patients with adult-onset PTD have abnormal SDTs; in this study, one of five affected family members fell within the normal range. The proportion of false-negative results may be 20%. The association of sensory tricks with abnormalities of spatial discrimination was not addressed in this study, but is worthy of examination in a larger dystonia cohort. Only one of eleven unaffected siblings had an abnormal SDT, but they came from three sibships of 15 individuals, four of whom were clinically affected but over 45 years. Abnormal SDTs were found in six of 13 children and five of 25 second-degree relatives, consistent with autosomal dominant inheritance. If an abnormal SDT in an at-

risk family member is an endophenotype, then the possibility of linkage analysis is increased by assigning carrier status to both the clinically affected family members and those with abnormal SDT results.

References

1. Stojanovic M, Cvetkovic D, Kostic VS. A genetic study of idiopathic focal dystonias. *J Neurol* 1995;242:508–511.
2. Leube B, Kessler KR, Goecke T, et al. Frequency of familial inheritance among 488 index patients with idiopathic focal dystonia and clinical variability in a large family. *Mov Disord* 1997;12:1000–1006.
3. Tinazzi M, Rosso T, Fiaschi A. Role of the somatosensory system in primary dystonia. *Mov Disord* 2003;18:605–622.
4. Bara-Jimenez W, Shelton P, Hallett M. Spatial discrimination is abnormal in focal hand dystonia. *Neurology* 2000;55:1869–1873.
5. Molloy FM, Carr TD, Zeuner KE, et al. Abnormalities of spatial discrimination in focal and generalised dystonia. *Brain* 2003;126:2175–2182.
6. Meunier S, Garnerio L, Ducorps A, et al. Human brain mapping in dystonia reveals both endophenotypic traits and adaptive reorganisation. *Ann Neurol* 2001;50:521–527.
7. Garraux G, Bauer A, Hanakawa T, et al. Changes in brain anatomy in focal hand dystonia. *Ann Neurol* 2004;55:736–739.
8. O’Riordan S, Raymond D, Lynch T, et al. Age at onset as a factor in determining the phenotype of primary torsion dystonia. *Neurology* 2004;63:1423–1426.
9. Edwards MJ, Huang Y-Z, Wood NW, et al. Different patterns of electrophysiological deficits in manifesting and non-manifesting carriers of the *DYT1* gene mutation. *Brain* 2003;126:2074–2080.
10. Eidelberg D, Moeller JR, Antonini A, et al. Functional brain networks in *DYT1* dystonia. *Ann Neurol* 1998;44:303–312.

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