Sporadic adult onset dystonia: sensory abnormalities as an endophenotype in unaffected relatives

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SHORT REPORT

Sporadic adult onset dystonia: sensory abnormalities as an endophenotype in unaffected relatives

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Background: Most patients with adult onset primary torsion dystonia (AOPTD) have the sporadic form of the disease. They may however be the only manifesting family members of a poorly penetrant genetic disorder. Sensory changes, including structural abnormalities of the primary sensory cortex, are found in AOPTD. Spatial discrimination threshold (SDT), a measure of sensory cortical organisation, is abnormal in AOPTD and in unaffected relatives of patients with familial AOPTD. Our hypothesis was that abnormal SDTs might be found in unaffected relatives of patients with sporadic AOPTD.
Methods: SDTs were assessed at the index finger bilaterally by a grating orientation task. Normal age related SDTs were derived from 141 control subjects aged 20–64 years. SDTs were considered abnormal when greater than 2.5 SD above the control mean. In total, 105 of 171 (61%) eligible unaffected siblings and offspring of patients with cervical dystonia had SDT examined.
Results: Fourteen of 48 siblings (29%) and 10 of 57 (18%) offspring were found to have an abnormal SDT. Only five of the 20 patients examined had abnormal SDTs. In 11 of the 25 families, no abnormality was found in an unaffected relative. In the 14 families where at least one unaffected relative had an abnormal SDT, 14 of 37 siblings (38%) and 10 of 33 offspring (30%) had abnormal SDTs.
Conclusion: Sensory abnormalities found in unaffected relatives of patients with apparently sporadic AOPTD may be a surrogate marker for the carriage of an abnormal gene.

Despite advances in our understanding of the pathophysiology of primary torsion dystonia, its genetic aetiology remains largely unknown. This is particularly true for the adult onset focal and segmental forms, including cervical dystonia, for which no causative gene has been identified.[1] Early onset generalised primary torsion dystonia is transmitted in an autosomal dominant fashion with a reduced penetrance of between 30% and 40%,[2] the majority of cases being due to a deletion in the DYT1 gene on chromosome 9q34.[3] Studies of multiplex families with adult onset primary torsion dystonia (AOPTD) also indicate an autosomal dominant pattern of inheritance with an estimated penetrance of 12–15%.[4] Alternatively, penetrance may be higher in some families with the remainder being non-genetic.[5–7] Identification of the genetic cause of AOPTD has been difficult because informative families are rare because of the low penetrance of the phenotype. In familial dystonia, absence of a structural or biochemical marker of carrier status makes it difficult to identify enough individuals and families to adequately power linkage analysis studies. Phenotypic heterogeneity, late age of onset and the unreliability of family history in AOPTD may further complicate the recognition of potentially informative families.[4 8 9]

Evidence from clinical, electrophysiological and neuroimaging studies has revealed the presence of somatosensory deficits which appear to have a primary role in the pathogenesis of dystonia.[10] Spatial discrimination threshold (SDT), measured at the fingertips using Johnson–Van Boven–Phillips (JVP) domes, is a measure of spatial acuity and is impaired in patients with focal hand dystonia, cervical dystonia and blepharospasm.[11 12] This abnormality is consistent with the bilateral cortical abnormalities demonstrated in AOPTD in which sensory fields are enlarged and overlapping.[13 14] If these observed sensory changes are a primary phenomenon, they might be present in gene carriers who have no clinical manifestations of dystonia and could therefore be regarded as an endophenotype.

We have previously shown the presence of abnormal SDTs in unaffected relatives aged 20–45 years old in four multiplex AOPTD families.[15] It is possible that a subset of patients with sporadic AOPTD are the only manifesting carriers of the poorly penetrant familial form of AOPTD. The hypothesis for this study was that abnormal SDTs may be found as an endophenotype in unaffected relatives of some patients with sporadic AOPTD.

METHODS

Control subjects

The control subjects were 141 healthy volunteers, aged 20–64 years old, recruited among health sciences students, hospital staff and visitors to the hospital. All gave a full clinical history and were examined. Exclusion criteria were the presence of any neurological abnormality or neuropathic symptoms, a history of cerebral, cervical or brachial injury, a medical illness known to cause neuropathy, the finding of digital callouses and the extended use of vibrating tools.

Patients with sporadic AOPTD and their unaffected relatives

Twenty-five patients with sporadic cervical dystonia were recruited from our movement disorders clinic. All had a focal dystonia without spread, with disease onset between 33 and 64 years of age. None had a family history of dystonia. In all cases a clinical diagnosis was made without testing for the DYT1 deletion as each patient's age of onset was after 30 years of age and none had a relative with early onset dystonia.[16] These patients had a total of 200 living siblings and offspring, of which 171 were eligible for SDT examination (eight were excluded because of an abnormal sensory examination and 21 were outside the 20–64 years age range). SDTs were examined in 20 of the 25 patients with AOPTD (five were older than 64 years of age), all of whom had received their usual therapeutic botulinum toxin injections within the previous 8 weeks. In total, 105 of 171 (61%) eligible siblings and offspring were tested, 48 siblings and 57 offspring. In all, dystonia was ruled out by a standardised clinical examination without video.[2]

Abbreviations: AOPTD, adult onset primary torsion dystonia; JVP, Johnson–Van Boven–Phillips; SDT, spatial discrimination threshold

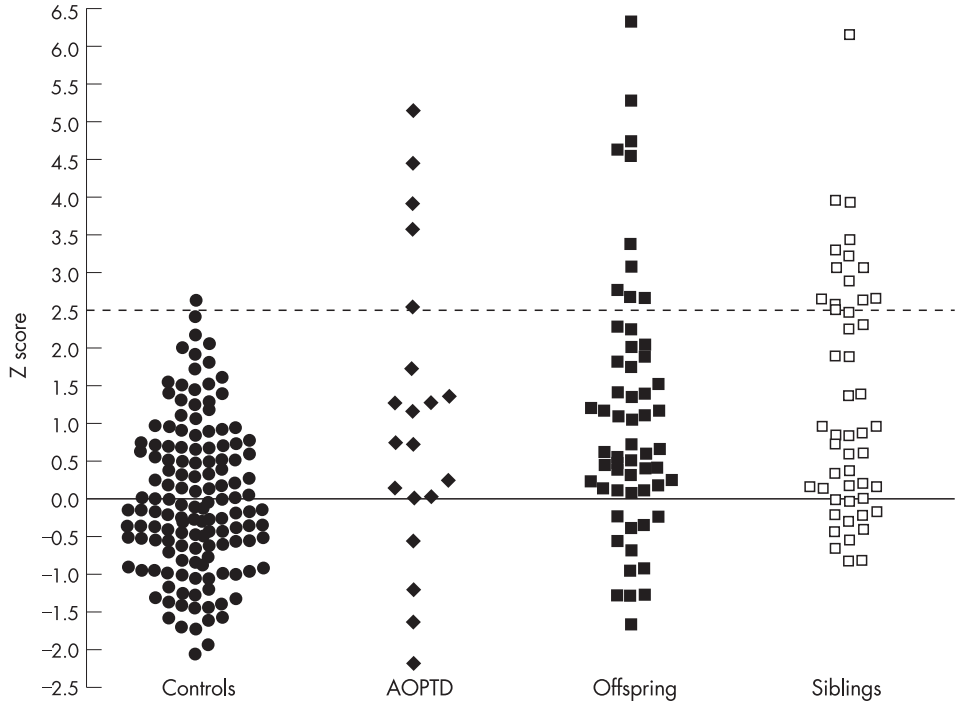

Figure 1 Spatial discrimination thresholds (SDTs) in the control group, patient group and in unaffected siblings and offspring. SDTs are represented as Z scores in 141 control subjects, 20 patients with cervical dystonia and 48 unaffected siblings and 57 unaffected offspring of affected individuals. All subjects were aged 20–64 years of age. The horizontal broken line represents a Z score of 2.5. AOPTD, adult onset primary torsion dystonia.

Sensory testing

SDT was measured using a grating orientation task employing a set of JVP domes (Stoelting Co., Illinois, USA). The standard set consists of eight hemispheric acrylic domes with parallel gratings of uniform width between 0.35 mm and 3.0 mm. A ceiling effect was noted in the control group at 45 years of age because of an age related deterioration in the peripheral nervous system. Four new domes with grating widths of 2.5 mm, 3.5 mm, 4.0 mm and 4.5 mm were added to establish normative data for a control population over 45 years of age.[17] A further ceiling effect was found at 65 years and therefore testing was limited to subjects below this age.

SDT was determined at the skin overlying the distal fat pad of both index fingers. Seated opposite the examiner, separated by

Table 1 Summary statistics of all 25 families examined, including age of onset and predominant nature of the cervical dystonia in each proband

Proband	Dystonia	Age of onset (y)	Total sibs and O/S	Eligible sibs and O/S	Examined	% eligible examined	Abnormal SDTs
1	R torticollis	60	8	5	3	60	2
2	L torticollis	33	8	6	6	100	3
3	R torticollis	45	14	10	4	40	0
4	L torticollis	48	2	2	1	50	0
5	L torticollis	36	7	4	3	75	0
6	L torticollis	45	4	3	1	33	1
7	R torticollis	45	4	2	1	50	0
8	L torticollis	64	6	3	2	66	0
9	R torticollis	46	12	11	7	64	3
10	R torticollis	65	5	4	3	75	2
11	R torticollis	60	11	8	5	63	1
12	R torticollis	64	8	6	2	33	0
13	L torticollis	52	16	10	6	60	0
14	R torticollis	46	6	6	4	66	0
15	L torticollis	57	11	7	4	57	2
16	Retrocollis	45	10	10	6	60	1
17	L torticollis	57	6	5	5	100	2
18	L torticollis	50	8	7	6	86	1
19	L torticollis	54	18	15	9	60	2
20	L torticollis	47	10	10	6	60	0
21	L laterocollis	47	6	6	6	100	1
22	L torticollis	41	5	5	5	100	0
23	R laterocollis	49	19	16	6	38	2
24	L torticollis	59	6	6	3	50	1
25	L saggital shift	38	4	4	1	25	0

L, left; O/S, offspring; R, right; SDT, spatial discrimination threshold; Sibs, siblings.

an opaque screen, the subject's finger was held in an extended position with the nail opposed against a firm surface on the examiner's side. Beginning with the largest grating width and proceeding through gradually narrower ones, the domes were applied to the skin for 1–2 s with enough pressure to indent the skin approximately 1 mm. Gratings were applied either perpendicular or parallel to the long axis of the finger. The blinded subject was required to identify the orientation immediately using a forced choice paradigm of ''down'' or ''across'' and received no feedback. There were 20 applications of each dome in a random order. The process continued until less than 60% of answers for a given grating width were correct. The SDT for each hand was calculated by linear interpolation of the 75% level of accuracy and the final SDT was calculated as the mean of both hands.[18] Mean SDTs and SDs were calculated for each of four control groups stratified by age: 20–29 years, 30–39 years, 40–49 years and 50–64 years. The mean (+2.5 SD) was taken as the upper limit of normal for each age group. Study subject SDTs were converted to Z scores; a Z score >2.5 was considered abnormal.

Ethics approval for this study was obtained from the Ethics and Medical Research Committee of St Vincent's University Hospital, Dublin, Ireland.

RESULTS

Control subjects

Spatial discrimination varied with age in the 141 control subjects examined. The mean (SD) SDTs for the control subjects were: for age group 20–29 years 1.172 (0.315) mm, for 30–39 years 1.051 (0.286) mm, for 40–49 years 1.465 (0.500) mm and for 50–64 years 1.851 (0.578) mm. The respective upper limits of normal (mean +2.5 SD) were therefore 1.959 mm, 1.766 mm, 2.716 mm and 3.297 mm for each group.

Sporadic AOPTD patients and unaffected relatives

Abnormal SDTs were found in five of the 20 (25%) tested patients with AOPTD. Twenty-four of the 105 unaffected relatives were found to have an abnormal SDT; 14 of 48 (29%) siblings and 10 of 57 (18%) offspring (fig 1). Abnormal SDTs were found in one or more unaffected relatives in 14 families and two or more relatives in eight families. In 11 of the 25 families, no SDT abnormalities were found in an unaffected relative (table 1). Exclusion of these 11 families left 14 families in which 34% of all examined relatives had abnormal SDTs, 14 of 37 (38%) siblings and 10 of 33 (30%) offspring.

DISCUSSION

We have shown that abnormalities of spatial acuity can be demonstrated in unaffected siblings and offspring of some patients with apparently sporadic AOPTD. We postulate that these sensory abnormalities represent an endophenotype which may or may not be expressed as a dystonia phenotype, possibly depending on other modifying genetic or environmental factors. Fourteen of 25 patients had one or more unaffected relatives with abnormal SDTs and we postulate that the proband in each family is the only manifesting gene carrier of an autosomal dominant focal dystonia. Those patients who had no relative in whom a sensory processing abnormality could be found may represent a disease phenocopy, carry a spontaneous mutation causing dystonia or may be manifesting a genetic variant of what is probably a complex genetic disorder.

The proportion of abnormal SDTs in the group of affected subjects was lower than expected. A disease endophenotype should presumably be fully penetrant in subjects who go on to manifest the full clinical phenotype. As stated, the proband in each family was regularly receiving botulinum toxin. This treatment may have an indirect effect on sensory cortical organisation via deafferentation of muscle spindles.[19 20] We have described an improvement in spatial discrimination thresholds in patients being treated for cervical dystonia.[21] Further study of SDTs before and after treatment in patients naïve to botulinum toxin is required. A ''perfect'' endophenotype for a presumed autosomal dominant disease would be found in 50% of unaffected first degree relatives. We found abnormal SDTs in 29% of siblings and 18% of offspring. Thus the penetrance of the SDT endophenotype is less than 100%. A difficulty with SDT testing is that it is an insensitive way of measuring changes in the sensory cortex because of age related changes in the innervation density of slowly adapting type 1 fibres (SA1) and their receptors, Merkel epidermal cells.[22] This prevents the assessment of individuals older than 64 years of age and causes a dispersion of the normal range in subjects older than 50 years of age, making it difficult to identify abnormalities in individuals in this age group. Other endophenotypes with a higher penetrance and specificity should be sought, the use of neuroimaging to directly demonstrate structural cortical abnormalities being a potential candidate. However, the advantages of SDT examination are that it is an inexpensive test which is easily performed and amenable to use out in the field for the examination of large pedigrees in the study of dystonia genetics.

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