Do primary adult-onset focal dystonias share aetiological factors?

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To consider whether the various clinical types of primary late-onset dystonia have a common aetiological background, or are each distinct and separate entities, sharing only the clinical appearance of dystonia, we reviewed epidemiological, clinical, neurophysiological and imaging data reported in patients with different forms of primary late-onset dystonia. The epidemiological and clinical features that distinguished the various clinical types and suggest aetiological differences were prevalence, age of onset, sex preference, sensory tricks, and tendency to spread. Likewise, aetiological differences were also supported by the observation that environmental risk factors possibly triggering focal dystonias in predisposed subjects can differ from one form to the other. The fact that different forms of focal dystonia may coexist in the same individual as the result of spread nevertheless suggests that the various focal dystonias are related. Detailed examination of available familial and genetic data indicates that the different forms of primary late-onset dystonia share aetiological factors, most probably genetic. Neurophysiological and imaging studies have demonstrated a number of abnormalities in focal dystonias and some of these are shared by the different clinical types. The shared abnormality of sensorimotor integration (and cortical excitability) beyond the symptomatic body part identified in various clinical types and in unaffected relatives might reflect the genetic abnormality indicating the substrate on which the dystonia develops.

Keywords: focal dystonia; complex disease; genetics; brain imaging; clinical neurophysiology

Abbreviations: BSP = blepharospasm; CD = cervical dystonia; FHD = focal hand dystonia; TMS = transcranial magnetic stimulation; EMG = electromyography; SMA = supplementary motor area; CSP = Cortical silent period; MEP = motor evoked potential; GABA = gamma amino butyric acid; fMRI = functional magnetic resonance imaging; PET = positron emission tomography; SPECT = single photon emission computed tomography


Introduction

Although dystonic conditions such as blepharospasmoromandibular dystonia, spasmodic torticollis and writer’s cramp were originally considered manifestations of psychiatric disorders, in the late 1970s Marsden and others proposed that these are neurological entities related to idiopathic torsion dystonia (Marsden, 1976a, b; Sheeny and Marsden, 1982; Fahn, 1988). Marsden also suggested that the various forms of focal dystonia have common clinical features and possibly originate from a basal ganglia disorder (Marsden, 1976a, b). A later study classified dystonia on the basis of aetiology (primary and secondary dystonia), age of onset (early- versus adult-onset dystonia), and body distribution (focal, segmental, multifocal, generalized and hemidystonia) (Fahn et al., 1988).

Primary adult-onset dystonia, the most common form of dystonia, has variable clinical expression, often focal onset [blepharospasm (BSP), oromandibular dystonia, cervical dystonia (CD), laryngeal dystonia or arm dystonia], and a limited tendency to spread to adjacent body regions
(Fahn et al., 1998). As the condition seems to aggregate within certain families, primary adult-onset dystonia is assumed to be partly genetic in origin (De Cavalho et al., 2002). Linkage studies identified mutations in the DYT1 gene and the DYT7 locus in a few large Mendelian families (Gasser et al., 1996; Leube et al., 1996; Bhidayasiri et al., 2005), but these findings are not present in most other families (suggesting genetic heterogeneity) or in apparently sporadic series (De Cavalho et al., 2002). Hence the gene(s) that possibly lend risk to commonly occurring adult-onset dystonia are not known. That the aetiology reflects combined genetic and environmental factors receives support from the transmission pattern consistent with either autosomal dominant trait and reduced penetrance or multifactorial inheritance (Waddy et al., 2001; Defazio et al., 1999; De Cavalho et al., 2002).

Numerous epidemiological and clinical features distinguish the various forms of primary adult-onset dystonias and suggest aetiological differences. Certain clinical features imply that the various focal dystonias may nevertheless be interrelated. Neurophysiological and imaging studies have also demonstrated a number of abnormalities in dystonias, some of which are shared by the different clinical types.

Proper classification is crucial for planning and designing sufficiently powered studies to assess the aetiology of the condition. In this review, to assess whether the various clinical types have a common aetiological background, or are each distinct and separate entities, sharing only the clinical appearance of dystonia (Berardelli, 2006), we reviewed epidemiological, clinical, familial/genetic and environmental risk factors studies as well as neurophysiological and imaging data on primary late-onset dystonias.

**Epidemiological data**

Methodological limitations notwithstanding, the available studies on the prevalence of primary adult-onset dystonia almost unanimously suggest that prevalence rates differ among the various focal types (Table 1). Studies from various geographic areas indicate that BSP and CD are more frequent than laryngeal and focal hand dystonia (FHD) (Defazio et al., 2004). International prevalence trends nevertheless seem discordant. In prevalence studies from the USA and Northern Europe CD was more frequent than BSP whereas in studies from Italy and Japan the trend was reversed, BSP being more frequent than CD (Matsumoto et al., 2003; Defazio et al., 2004). Owing to methodological problems from differences in ascertainment across studies (Defazio et al., 2004), however, we can draw few inferences about geographical variability in the prevalence of different forms of primary late-onset dystonia.

Among adult-onset focal dystonias, age of onset varies in a way suggesting that with increasing age the site of onset shifts caudorostrally (Table 1). Dystonic symptoms appear earlier in the upper limb and neck than in the face. A meta-analysis of major series of patients published in English literature in the past 25 years showed that the mean age of onset is 38 years for FHD, 41 years for CD, 43 years for laryngeal dystonia and 56 years for BSP (O’Riordan et al., 2004). Finally, dystonias in the craniocervical area are more common in women and occupational limb cramps in men (Soland et al., 1996) (Table 1).

**Clinical features**

Primary adult-onset dystonias are often focal at onset and may spread over time to adjacent body regions so that different forms coexist in the same individual. Notably, different sites of onset confer different risks of spread (Table 1). In more than half of patients presenting with BSP, dystonia usually spreads during the initial 5 years and then stabilizes; whereas fewer patients presenting with CD, laryngeal dystonia or FHD experience significantly less spread to adjacent body regions within 5 years (Greene et al., 1995; Defazio et al., 1999; Weiss et al., 2006). Whether the type and extent of spread differ in patients after 5 years remains unknown.

Sensory tricks that can ameliorate dystonic movements or posture in various parts of the body are a clinical feature of different focal dystonias, but the usefulness of sensory tricks differs among the various types. Sensory tricks are common in CD and less common in cranial and hand dystonia (Fahn, 1988; Filipovic et al., 2004).
An interesting feature that may distinguish laryngeal dystonia and FHD from other focal types is task specificity, namely when dystonia affects one task alone. Laryngeal dystonia is specific for speaking and can improve with singing (Schweinfurth et al., 2002). The most common task-specific FHD is writer’s cramp, but almost any task can be affected (Fahn et al., 1998). Other frequent task-specific hand dystonias are typist’s cramp and musician’s cramp, including pianist cramp, guitar cramp and flautist cramp (Frucht et al., 2001, Frucht, 2004). At times, when the disorder worsens, task specificity is lost, and dystonia can impair other tasks or even become spontaneous.

**Familial and genetic data**

Several large families with early-onset dystonia, late-onset dystonia or mixed phenotype (including cases with either early- or late-onset dystonia) have been reported. Our review identified 13 large families with exclusively late-onset primary dystonia (Table 2). Eight of these families were characterized by phenotypic heterogeneity, whereas five families included individuals suffering from the same type of dystonia, namely CD (one family), FHD (two families) and BSP (two families). Linkage analysis performed in some of these large families, identified the DYT1 gene in a family with FHD (Gasser et al., 1996), and the DYT7 locus in two families, one with CD and laryngeal dystonia, the other with FHD (Leube et al., 1995; Bhidayasiri et al., 2005). Linkage to DYT6 and DYT13 loci, originally found in families including cases of early- and late-onset dystonia, has never been described in families with pure late-onset dystonia (Munchau et al., 2000; Brancati et al., 2002; Defazio et al., 2003a).

In addition to large families with exclusively adult-onset focal dystonia, our review identified six clinical series based on clinical examination of first-degree relatives (Waddy et al., 1991; Defazio et al., 1993; Stojanovic et al., 1995; Leube et al., 1997; Martino et al., 2004; Defazio et al., 2006). In most cases, no more than one affected first-degree relative could be found. Meta-analysis of the four references giving extensive data on probands and affected relatives (Waddy et al., 1991; Stojanovic et al., 1995; Leube et al., 1997; Martino et al., 2004) yielded 71 proband-relative pairs, of whom 33 (46.5%) were phenotypically discordant, and 38 (53.5%) were phenotypically concordant. Stratifying by type of dystonia in the proband yielded significantly more discordant pairs when the proband suffered from CD or FHD than concordant pairs when the proband was affected by BSP (Table 3).

Regardless of phenotypic appearance, an inheritance pattern compatible with an autosomal dominant trait and reduced penetrance was apparent in a few large families (Munchau et al., 2000; Brancati et al., 2002; Defazio et al., 2003a). More often, however, the number of ascertained affected relatives is small, and inheritance does not appear to be Mendelian. A likely hypothesis is that adult-onset dystonias could represent a multifactorial condition, in which several genes, along with environmental factors, combine to reach the threshold of disease (De Cavalho et al., 2002).

**Table 2** Phenotype and results of linkage analysis in large families with exclusively primary late-onset dystonia

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Proband phenotype</th>
<th>Relative phenotype</th>
<th>Linkage analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utti et al., 1993</td>
<td>CD</td>
<td>CD</td>
<td>DYT1 excluded</td>
</tr>
<tr>
<td>Micheli et al., 1994</td>
<td>FHD</td>
<td>FHD, CD</td>
<td>Not checked</td>
</tr>
<tr>
<td>Bressman et al., 1996</td>
<td>CD</td>
<td>CD, CD/FHD</td>
<td>DYT1 excluded</td>
</tr>
<tr>
<td>Gasser et al., 1996</td>
<td>FHD</td>
<td>FHD</td>
<td>DYT1</td>
</tr>
<tr>
<td>Cassetta et al., 1999</td>
<td>BSP</td>
<td>BSP, CD, OMD</td>
<td>DYT1, DYT6, DYT7 excluded</td>
</tr>
<tr>
<td>Munchau et al., 2000</td>
<td>CD</td>
<td>CD, laryngeal dystonia</td>
<td>DYT1, DYT6, DYT7 excluded</td>
</tr>
<tr>
<td>Leube et al., 1996</td>
<td>CD</td>
<td>BSP, CD, FHD</td>
<td>DYT1, DYT6, DYT7, DYT13 excluded</td>
</tr>
<tr>
<td>Brancati et al., 2002</td>
<td>CD</td>
<td>BSP</td>
<td>DYT1, DYT6, DYT7, DYT13</td>
</tr>
<tr>
<td>Defazio et al., 2003a</td>
<td>BSP</td>
<td>BSP</td>
<td>DYT1, DYT6, DYT7, DYT13</td>
</tr>
<tr>
<td>Family 1</td>
<td>BSP</td>
<td>BSP</td>
<td>DYT1, DYT6, DYT7, DYT13</td>
</tr>
<tr>
<td>Family 2</td>
<td>BSP</td>
<td>BSP</td>
<td>DYT1, DYT6, DYT7, DYT13</td>
</tr>
<tr>
<td>Jimenez-Jimenez et al., 2002</td>
<td>BSP</td>
<td>BSP, OMD, CD</td>
<td>Not checked</td>
</tr>
<tr>
<td>O’Riordan et al., 2004</td>
<td>CD/HD</td>
<td>FHD, CD/FHD</td>
<td>Not checked</td>
</tr>
<tr>
<td>Bhidayasiri et al., 2005</td>
<td>FHD</td>
<td>FHD</td>
<td>DYT7</td>
</tr>
</tbody>
</table>

**Table 3** Distribution of phenotypically concordant and discordant proband—relative pairs according to the dystonia phenotype in the proband

<table>
<thead>
<tr>
<th>Proband phenotype</th>
<th>Relative phenotype</th>
<th>Concordant</th>
<th>Discordant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharospasm</td>
<td>12</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Cervical dystonia</td>
<td>23</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Hand dystonia</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Data were from 71 pairs from four familial series. $\chi^2$: 746; $P = 0.024$. 

BSP = blepharospasm; CD = cervical dystonia; OMD = oromandibular dystonia; FHD = focal hand dystonia.
Environmental risk factors

Two case–control studies (Defazio et al., 1998; Martino et al., 2005) found a significant association between BSP and diseases of the anterior segment of the eye (blepharitis, keratoconjunctivitis and dry eye). In one study the strength of the association increased when eye diseases first manifested around the fifth and sixth decades (Martino et al., 2005). As this age range corresponds to the peak age of incidence of BSP, and to the beginning of the physiological decline in the dopaminergic control upon the trigeminal blink reflex circuit, it might represent a temporal window of relative vulnerability to ocular diseases triggering BSP (Peshori et al., 2001; Evinger et al., 2002). Supporting the association between BSP and dry eye, a Japanese study reported the frequency of BSP among subjects suffering from dry eye as 8.1% (Tsubota et al., 1997). This figure is higher than the estimated prevalence of primary BSP in the Japanese population of the same age group (Matsumoto et al., 2003). Eye diseases were not associated with dystonia other than BSP (Defazio et al., 1998).

There have been anecdotal observations of oromandibular dystonia occurring shortly after an injury or a surgical intervention at the faciobuccal area (Sankhla et al., 1998; Schrag et al., 1999), but no controlled study assessed the issue.

Patients with focal laryngeal dystonia, often have a history of a sore throat. A case–control study confirmed the clinical observation (Schweinfurth et al., 2002). Several uncontrolled clinical investigations (Jankovic, 2001) and one case–control study (Defazio et al., 1998) suggested a relationship between prior neck–trunk trauma and CD. Two case-control studies found a higher frequency of idiopathic scoliosis in CD than in control patients (Duane, 1998; Defazio et al., 2003b). Neither neck–trunk trauma nor idiopathic scoliosis were associated with cranial dystonia (Defazio et al., 1998; Martino et al., 2006).

To date no controlled study has specifically focused on risk factors for hand dystonia. Nevertheless, obvious evidence links FHD with working activities that require repetitive and accurate motor tasks (Fruch, 2004). Altenmuller estimated the prevalence of FHD among musicians to be as high as 0.5% of 10,000 performing German musicians (Fruch, 2004), whereas the prevalence of the condition in the general population ranged between 3.8 and 80 cases per million across different studies (Defazio et al., 2004). Two observations further supported a role of activity at work for the development of task-specific FHD among musicians (Frucht et al., 2004). First, patients often date the onset of dystonia to an increase in practice time, change in technique, or an attempt to undertake a challenging repertoire. Second, dystonia is more likely to develop in the hand that performs the more complex task.

Neurophysiological abnormalities

A number of neurophysiological abnormalities have been demonstrated at various levels of motor and sensory system in patients with focal dystonia (Berardelli et al., 1998). For the purpose of this study, we will review only the neurophysiological investigations performed in more than one form of focal dystonia and also body segments clinically unaffected by dystonia (Table 4).

With the paired-pulse method of TMS an initial conditioning subthreshold stimulus activates cortical neurons and, at intervals of <5 ms, inhibits the size of a second suprathreshold test stimulus (‘intracortical inhibition’) (Curià et al., 2002). This inhibition is largely a GABA-A effect. Intracortical inhibition is reduced in patients with FHD on both affected and unaffected hand (Ridding et al., 1995; Gilio et al., 2000) and decreased intracortical inhibition related to hand muscles has also been reported in patients who have BSP without hand dystonia (Sommer et al., 2002). The decreased intracortical inhibition suggests

### Table 4 Results of studies applying neurophysiological tests to different forms of primary late-onset dystonia

<table>
<thead>
<tr>
<th>Test</th>
<th>Cranial dystonia</th>
<th>Cervical dystonia</th>
<th>Focal hand dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMS with paired pulse</td>
<td>Reduced intracortical inhibition in hand muscles</td>
<td>Not done (to check)</td>
<td>Reduced intracortical inhibition in hand muscles</td>
</tr>
<tr>
<td>TMS assessing cortical silent period</td>
<td>Shortened cortical silent period in cranial muscles</td>
<td>Shortened cortical silent period in cervical and cranial muscles</td>
<td>Shortened cortical silent period in the hand muscles</td>
</tr>
<tr>
<td>Blink reflex</td>
<td>Reduced inhibition of the R2 component</td>
<td>Abnormal RI in hand muscles</td>
<td>Normal inhibition of the R2 component</td>
</tr>
<tr>
<td>Reciprocal inhibition (RI)</td>
<td>Normal</td>
<td>Abnormal RI in hand muscles</td>
<td>Abnormal RI in hand muscles</td>
</tr>
<tr>
<td>Testing of temporal somatosensory discrimination</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Testing of spatial somatosensory discrimination</td>
<td>Raised threshold on both hands</td>
<td>Not done (to check)</td>
<td>Raised threshold on both hands</td>
</tr>
<tr>
<td>MEP inhibition induced by median nerve stimulation</td>
<td>Not done (to check)</td>
<td>Raised threshold on both hands</td>
<td>Raised threshold on both hands</td>
</tr>
</tbody>
</table>

TMS = transcranial magnetic stimulation; MEP = motor-evoked potential.
increased excitability of the cortical hand motor area. One consequence of decreased inhibition is a loss of surround inhibition that could explain the overflow phenomenon seen in patients with dystonia (Sohn and Hallett, 2004). The cortical silent period (CSP) is another marker of cortical motor excitability that can be studied by TMS. The CSP is a pause in the ongoing voluntary EMG activity elicited by a single magnetic stimulus and is mediated by GABA-B receptors (Werhahn et al., 1999). The duration of the CSP is reduced in the affected muscles of patients with cranial, cervical and hand dystonia (Rona et al., 1998; Curra et al., 2000). In patients with BSP, the SP was also shortened in perioral muscles (Currà et al., 2000) but not in cervical and hand muscles (Cakmur et al., 2004); in patients with cervical dystonia, the CSP was shortened in cranial muscles, in the sternocleidomastoid muscles of both the affected and unaffected sides, but not in hand muscles (Cakmur et al., 2004); and in patients with FHD, the CSP was shortened in both the affected and unaffected hand (Rona et al., 1998).

With paired associative stimulation (PAS) a nerve shock is paired with a TMS pulse to the sensorimotor cortex, and the resultant increase in motor-evoked potential (MEP) size is thought to reflect the long-term potentiation of excitatory synapses (Stephan et al., 2000). PAS produces a larger increase in MEP size and less spatial specificity in patients with FHD than in normal subjects (Quartarone et al., 2003). PAS abnormalities are also present when patients imagine the movement without actually performing it (Quartarone et al., 2005).

In patients with cranial dystonia, studies of the orbicularis oculi muscles have shown reduced inhibition of the R2 component of the blink reflex tested with the paired-pulse technique (Berardelli et al., 1985, 1999). This finding suggests increased excitability of the brainstem interneurons mediating the orbicularis oculi muscles reflex. Blink-reflex testing discloses similar abnormalities in patients with CD but not in patients with FHD (Paulletti et al., 1993).

Ia reciprocal inhibition between agonist and antagonist muscles is reduced in patients with FHD (Panizza et al., 1989; Priori et al., 1995), in patients with CD, but not in patients with BSP (Panizza et al., 1990; Deuschl et al., 1992). Abnormalities of Ia inhibition suggest that dystonia leads to altered processing of afferent input to the spinal cord or abnormal supraspinal control of the spinal interneurons mediating presynaptic inhibition in the spinal cord.

Although no sensory loss is apparent clinically, detailed testing of temporal and spatial discrimination threshold of somatosensory stimuli (defined as the shortest time/spatial interval at which two stimuli are perceived as separate) discloses abnormalities. For example, a raised somatosensory temporal discrimination threshold was detected in patients with CD and FHD (Bara-Jimenez et al., 2000a; Sanger et al., 2001; Fiorio et al., 2003), in the unaffected hand of patients with unilateral FHD (Fiorio et al., 2003) and in early-onset generalized DYT1 dystonia (Tinazzi et al., 2006, unpublished observation). These findings differ slightly from those obtained on spatial discrimination: raised somatosensory spatial discrimination threshold was found on both hands of patients with unilateral FHD, on hands of patients with CD and BSP, and also in unaffected first-degree relatives of CD patients (Bara-Jimenez, 2000b; Tinazzi et al., 2000; Fiorio et al., 2003; O’Dwyer et al., 2005). Sensory dysfunction can also be demonstrated with somatosensory evoked potential testing (Bara-Jimenez et al., 1998). The dipoles of the N20 from stimulation of individual fingers show disordered representation in the primary sensory cortex (Bara-Jimenez et al., 1998) and these abnormalities are present on both hands of patients with FHD (Meunier et al., 2001). Further evidence of abnormal sensorimotor integration comes from a study investigating the effect of peripheral stimulation on MEPs evoked by TMS. The inhibitory effect normally induced by median nerve stimulation is lost in patients with FHD but not in patients with CD (Abbruzzese et al., 2001).

### Imaging studies

Studies using various imaging techniques have reported abnormalities in several forms of adult-onset focal dystonia. For the purposes of this review, we focused on techniques used in more than one form of focal dystonia (Table 5).

Volumetric imaging studies of the basal ganglia showed significantly larger (~10%) putamina in patients with cranial and FHD than in healthy controls (Black et al., 1998). Studies using voxel-based morphometry in patients with BSP, CD and FHD showed changes in grey matter density in several brain areas (Draganski et al., 2003; Garraux et al., 2004; Etgen et al., 2006). A common finding was a bilateral increase in grey matter density in primary somatosensory and motor cortex. Major abnormalities in subcortical structures such as basal ganglia have been detected so far only in BSP and CD (Draganski et al., 2003; Etgen et al., 2006).

Hyperechogenic lesions in the basal ganglia (particularly the lenticular nucleus) were found in a significant proportion of patients with CD (75%) and FHD (83%) and also in one-third of the patients with facial dystonia. Abnormalities were not detected in secondary dystonias (Becker et al., 1997).

Functional magnetic resonance imaging (fMRI) studies showed that, in the absence of a specific dystonia-inducing task, patients with BSP and FHD have overactivity of the primary sensorimotor cortex and the caudal part of SMA (Oga et al., 2002; Baker et al., 2003; Dresel et al., 2006).

Functional MRI has also been used to explore the patterns of brain activation under specific dystonia-inducing tasks in patients with different types of hand dystonia. Common findings were overactivation in cerebellum and premotor areas (Berg et al., 2000;
Pujol et al., 2000; Preibisch et al., 2001). A recent study performed in patients with FHD showed a bilateral enhanced response of putamen, caudate nucleus, internal globus pallidus and lateral thalamus to tactile input from the affected hand during a dystonia-inducing task (Peller et al., 2006). In patients with cranial dystonia (BSP plus oromandibular dystonia), fMRI showed overactivation of the primary sensorimotor cortex and the caudal part of supplementary motor area (15)O-PET blood flow scans analysed sensorimotor processing in patients with writer’s cramp and BSP. In writer’s cramp, vibration of either the ‘affected’ or ‘unaffected’ hand produced a significantly reduced response to vibration of affected and unaffected body parts in primary sensorimotor area (Fahn et al., 1988). Yet insofar as different forms of focal dystonia may coexist in the same individual as the result of spread (Greene et al., 1995; Defazio et al., 1999; Weiss et al., 2006) and effectiveness of sensory tricks in relieving spasms (Fahn et al., 1988). The intrafamilial variability in the clinical expression of dystonia that characterizes many families with late-onset dystonia (Table 2) raises the possibility that the same susceptibility genetic factor(s) contribute to different clinical manifestations. Conversely, the report of families characterized by the same dystonia type suggests distinct

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**Table 5** Results of studies applying imaging tools to different forms of primary late-onset dystonia

<table>
<thead>
<tr>
<th>Test</th>
<th>Cranial dystonia</th>
<th>Cervical dystonia</th>
<th>Focal hand dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volumetric imaging</td>
<td>Putaminal enlargement</td>
<td>Not done (to check)</td>
<td>Putaminal enlargement</td>
</tr>
<tr>
<td>Voxel based morphometry</td>
<td>Bilateral increase in grey matter density in putamen and left parietal lobule</td>
<td>Bilateral increase in grey matter density in primary sensorimotor cortex</td>
<td>Bilateral increase in grey matter density in primary sensorimotor cortex</td>
</tr>
<tr>
<td>Transcranial sonography</td>
<td>Hypercentogenic lesions in the lenticular nucleus</td>
<td>Hypercentogenic lesions in the lenticular nucleus</td>
<td>Hypercentogenic lesions in the lenticular nucleus</td>
</tr>
<tr>
<td>fMRI in the absence of dystonia-inducing task</td>
<td>Overactivation of the primary sensorimotor cortex and the caudal part of supplementary motor area</td>
<td>Not done (to check)</td>
<td>Overactivation of the primary sensorimotor cortex and the caudal part of supplementary motor area</td>
</tr>
<tr>
<td>fMRI under dystonia-inducing task</td>
<td>Overactivation of primary sensorimotor cortex and supplementary motor area; deficient activation of primary motor and ventral premotor cortex within the mouth representation area</td>
<td>Not done (to check)</td>
<td>Overactivation of premotor cortex within the hand representation area</td>
</tr>
<tr>
<td>H2 (15)O-PET blood flow scan</td>
<td>Reduced response to vibration of affected and unaffected body parts in primary sensorimotor area</td>
<td>Not done (to check)</td>
<td>Reduced response to vibration of affected and unaffected body parts in primary sensorimotor area</td>
</tr>
<tr>
<td>SPECT</td>
<td>Bilateral reduction of post-synaptic dopamine D2 receptor binding in the striatum</td>
<td>Bilateral reduction of post-synaptic dopamine D2 receptor binding in the striatum</td>
<td>Bilateral reduction of post-synaptic dopamine D2 receptor binding in the striatum</td>
</tr>
</tbody>
</table>

fMRI = functional magnetic resonance imaging; PET = positron emission tomography; SPECT = single photon emission computed tomography.

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Receptor-binding functional imaging studies (SPECT/PET) documented a bilateral reduction of postsynaptic dopamine D2 receptor binding in the striatum of patients with the main forms of late-onset dystonia including cranial, cervical and hand dystonia (Hierholzer et al., 1994; Horstink et al., 1997; Perlmutter et al., 1997; Naumann et al., 1998).

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**Discussion**

Numerous epidemiological and clinical features distinguish the various forms of primary adult-onset dystonia and suggest aetiological differences. Features that differ most among the dystonic subtypes are prevalence (Defazio et al., 2004), age of onset (O’Riordan et al., 2004), sex distribution (Soland et al., 1996), tendency to spread (Greene et al., 1995; Defazio et al., 1999; Weiss et al., 2006) and effectiveness of sensory tricks in relieving spasms (Fahn et al., 1988). Yet insofar as different forms of focal dystonia may coexist in the same individual as the result of spread (Greene et al., 1995; Defazio et al., 1999; Weiss et al., 2006), the various focal dystonias may be interrelated.
genetic entities. The cross-sectional approach of available family studies and the variable age of onset of the various clinical types (O’Riordan et al., 2004) nevertheless leave open the possibility that families with apparently homogeneous dystonia will become phenotypically heterogeneous on follow up. Meta-analysis of proband-relative pairs from four family studies (Waddy et al., 1990; Stojanovic et al., 1995; Leube et al., 1997; Martino et al., 2004) indicated that the families with less evident phenotypic variability tended to have CD and FHD rather than BSP. Since CD/FHD usually develop earlier than cranial dystonia (O’Riordan et al., 2004), relatives of patients with CH/FHD may be younger on average than the relatives of patients with BSP. Even though no family study provided age data on the unaffected relatives, the greater phenotype homogeneity of families with CD and FHD might reflect the smaller number of subjects being at the age at risk for developing cranial dystonia rather than differences in genetic susceptibility between cranial and extracranial dystonia.

The results of linkage studies identifying the DYT1 gene in a family with FHD (Gasser et al., 1996) and the DYT7 locus in two families, one with FHD (Bhidayasiri et al., 2005), the other with CD/laryngeal dystonia (Leube et al., 1996), support the possibility that, even within a background of genetic heterogeneity, the same susceptibility genetic factor(s) contribute to different clinical manifestations. Notably, a similar scenario has been observed in other forms of dystonia such as DYT1 dystonia and dopa-responsive dystonia in which the same susceptibility genetic factor contributes to an array of clinical manifestations (De Cavalho et al., 2002). In most adult-onset dystonia families, inheritance does not appear to be Mendelian but is rather consistent with a multifactorial trait, in which several genes, along with environmental factors, concur to reach a threshold of disease (De Cavalho et al., 2002). If so, we can hypothesize that a certain number of genes are common to the various clinical types, with other specific genes or environmental factors, or both, contributing to the variability of clinical expression.

Although the body of work on the environmental risk factors leading to focal dystonia in predisposed subjects is limited, available evidence suggests that such factors can differ from one form to the other. Especially important, the frequency of environmental factors thought to trigger different focal dystonias may vary with age and sex. For instance, dry eye syndrome possibly triggering BSP (Defazio et al., 1998; Martino et al., 2005) is characterized by a slight female preponderance (estimated by an age-adjusted odds ratio around 1.5) and an increasing prevalence with increasing age (Schaumberg et al., 2003; Moss et al., 2004); idiopathic scoliosis that may precede CD usually develops before or at around the puberty and most frequently affects females (Reamy and Slakey, 2001); and certain activities engaged in at work that may contribute to FHD can be performed differently by men and women. The epidemiological differences in prevalence, age of onset and sex distribution among clinical subtypes might therefore arise, at least in part, from age- and sex-related differences in the frequency distribution of specific environmental risk factors.

If patients with different late-onset primary dystonias share at least some genetic susceptibility factors, then these patients should have detectable neurophysiological or imaging abnormalities, or both, that reflect the genetic abnormality and indicate the substrate on which the dystonia develops regardless of the variable phenotype. Possibly, these abnormalities should be detectable also in gene carriers who are not expressing the clinical symptoms. Although the body of neurophysiological and imaging studies applying the same technique to different forms of focal dystonia is limited, available data indicate that the most common subtypes, that is FHD, CD and BSP, may share neurophysiological and imaging abnormalities. Shared neurophysiological findings include (i) the impaired inhibitory control of motor mechanisms (at various levels of central nervous system) that may extend beyond the affected muscles (but not very far, with distant muscles being less influenced than those that are closer) and (ii) the abnormally raised somatosensory spatial and temporal discrimination threshold. Shared imaging abnormalities include (i) enlargement of putamina; (ii) hyperechogenic lesions in the lenticular nucleus; (iii) reduction of post-synaptic dopamine D2 receptor binding in the striatum; (iv) increase in grey matter density in the primary sensory cortex; (v) overactivity of the primary sensorimotor cortex and the caudal part of SMA disclosed by fMRI studies performed in the absence of a dystonia-inducing task; and (vi) abnormally reduced activity of the primary sensorimotor cortex after vibrotactile stimulation of affected and unaffected body areas.

There is evidence suggesting that some of these abnormalities may be primary, rather than the consequence of dystonic activity, and specific to late-onset dystonia. The spatial discrimination threshold was found to be abnormal on both hands of patients with unilateral hand dystonia and also on hands of patients with CD and BSP (Bara-Jimenez et al., 2000b; Tinazzi et al., 2000; Molloy et al., 2003; O’Dwyer et al., 2005). Likewise, physiological changes in the periorbital cortex outlined by fMRI were observed in both the affected and unaffected hand of patients with FHD as well as in the unaffected hands of patients with BSP (Dresel et al., 2006); and the reduced activation of cortical areas following vibrotactile stimulation was documented also for body areas not affected by dystonia, albeit to a smaller extent (Tempel and Perlmuter, 1993). Overall, these findings raise the possibility that abnormalities in the processing of sensory information and, possibly, of sensorimotor integration represent a specific endophenotypic trait. Supporting this view, the spatial discrimination threshold was abnormal in unaffected relatives of patients with adult-onset CD (O’Dwyer et al., 2005). These observations make it
necessary to check whether similar abnormalities are also present in unaffected relatives of patients with other forms of adult-onset dystonia.

The mechanisms underlying abnormalities in the processing of sensory information in late-onset dystonia are unknown. Tentatively, these abnormalities may be explained in light of the relationships between dystonia and dysfunctions of basal ganglia, implicated not only in motor control, but also in somatosensory processing (Lacruz et al., 1991; Artieda et al., 1992; Harrington et al., 1998). Support to this view comes from a recent fMRI study in patients with FHD (Peller et al., 2006). The study showed an enhanced response of the basal ganglia to tactile input from the affected hand. This is compatible with the concept of impaired centre-surround inhibition within the basal ganglia–thalamic circuit possibly leading to an excessive activation of sensorimotor cortical areas during skilled movements affected by dystonia. As the sensory system plays an important role in driving the motor system and abnormal sensation can lead to disordered movements (Hallett, 1995; Byl et al., 1996; Abruzzese and Berardelli, 2003), sensory system abnormalities might have a fundamental role in the pathophysiology of primary late-onset dystonias. If sensory abnormalities reflect the substrate on which the dystonia develops regardless of the variable phenotype, then factors inducing overload of the sensory system in a certain body area may trigger topographically related focal dystonia. A role for peripheral mechanisms in dystonia is also suggested by the neurophysiological findings obtained with the PAS technique, which combines peripheral and central stimulation. PAS findings highlight the possibility that environmental risk factors acting through peripheral mechanisms are important in triggering dystonia. One example is the repetitive motor activity thought to trigger some types of hand dystonia including musician’s dystonia and writer’s cramp. Another example may be the eye diseases that frequently precede BSP (Defazio et al., 1998; Martino et al., 2005). Likewise, an animal model of BSP supports a combination of genetic and environmental factors, with prolonged conjunctival irritation triggering the development of eyelid spasms (Schicatano et al., 1997). In another animal model (Byl et al., 1996), monkeys were trained to hold a vibrating manipulandum for long periods. After some time, they became unable to do so, and a motor control abnormality developed that was interpreted as a possible hand dystonia (even though the motor disorder was not task specific and involuntary muscle spasms were not documented). These monkeys all had unusually large sensory receptive fields in the cortex. These results implied that the synchronous sensory input caused an enlargement of the receptive field and the abnormal sensory function led to abnormal motor function. In human focal dystonia an overload of a predisposed sensory system by peripheral injury or repetitive motor activity in a certain part of the body, or by both, might cause sensory receptive changes in the corresponding cortical brain areas leading to abnormal regulation of inhibitory interneuronal mechanisms at brainstem or spinal cord level. Although degradation of the cortical sensory representation areas has been documented in patients with FHD (Abruzzese and Berardelli, 2003), we cannot be sure that this hypothetical mechanism would apply to FHD as well as to other focal dystonias in humans. Notably, because it should indicate profitable research areas, the literature review of tests applied to the various primary late-onset dystonias also identified specific neurophysiological changes (e.g. different behaviour of the MEP after median nerve stimulation in FHD and CD) and imaging abnormalities (e.g. different patterns of brain activation under specific dystonia-inducing motor tasks in patients with cranial and hand dystonia) that might reflect distinct pathophysiological mechanisms possibly related, at least in part, to differences in the physiological motor control of cranial and extracranial muscles. What is therefore needed are controlled studies assessing the association between repetitive motion or awkward prolonged postures of a certain part of the body and topographically related focal dystonias, and studies checking the cortical sensory representation areas in dystonias other than FHD.

Conclusions

Available familial, neurophysiological and imaging evidence raises the possibility that primary adult-onset focal dystonia is multifactorial in origin and that the various clinical forms share aetiopathological factors, most probably genetic. Support for a common genetic background comes first from the intrafamilial phenotypic heterogeneity, and also from the observed linkage of the same locus (DYT7) to families with different clinical manifestations. Further support comes from the observation that shared pathophysiological features predominate over differences. The shared abnormality in sensorimotor integration (and cortical excitability) in affected and unaffected body parts identified in various clinical types and in unaffected relatives might reflect the genetic abnormality indicating the substrate on which the dystonia develops. The observation that environmental risk factors differ among the various forms of focal dystonia suggests that the various clinical types may also differ in aetiology.

Our hypothesis is that a number of common genes underlie the pathophysiological mechanisms shared by the various forms of adult-onset focal dystonia and that additional genes or environmental factors or both determine the clinical, neurophysiological and imaging differences described in the various forms of dystonia. One way to test this hypothesis could be to search for common genes in the overall population of adult-onset dystonia regardless of phenotypic heterogeneity (Defazio et al., 2006), and then investigate whether other genes or environmental factors or both exist and are specific for each single form of
adult-onset focal dystonia. Our basic notion is that the focal dystonias are related multifactorial disorders and not simple Mendelian traits.

References


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