

## REVIEW ARTICLE

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# Current concepts on the clinical features, aetiology and management of idiopathic cervical dystonia

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### Summary

*Idiopathic cervical dystonia (ICD) is the most common form of adult-onset focal dystonia. Previously, disagreement existed about whether ICD was a psychiatric illness, but the disorder is now viewed as a neurological illness and large clinical series have clarified the clinical features of the disease. At the time of diagnosis, extracervical dystonia is found in ~20% of patients, and there may be a concomitant head or hand tremor. Importantly, adult-onset ICD does not become generalized, although there may be segmental spread and pain may increase independently of the dystonia. While 10–20% of patients may experience remission, nearly all patients relapse within 5 years and are left with persistent disease. The aetiology of ICD is unknown, but there has been much progress in clarifying the genetic abnormality in families with inherited adult-onset cervical dystonia; linkage to chromosome 18p has been demonstrated in one family, and the DYT1 locus has been excluded in two other families. Painful trauma may be involved in the pathogenesis of ICD. Painful stimuli are received and processed by the basal*

*ganglia, and the synaptic changes provoked by pain may lead to the abnormal physiology underlying dystonia. Consistent with this idea are experiments which demonstrate that altered sensory input leads to plasticity of the motor cortex, and those that explore the 'tonic vibration reflex' in patients with dystonia. Another theory suggests that a primary vestibular abnormality is responsible for ICD. Botulinum toxin is the most effective treatment for ICD. Roughly 75% of patients improve, and a response is generally seen within the first week. However, many questions remain regarding the optimal technique of administration. The development of neutralizing antibodies occurs in at least 5–10% of patients, and appears to be related both to dosage and to the interval between treatments. Side-effects are generally mild and result from the action of the toxin in the periphery. If the response to botulinum toxin is not adequate, anticholinergics, benzodiazepines, baclofen and other medications are used as adjunctive therapy. Surgical therapies are available for the treatment of ICD but are reserved for patients refractory to conservative measures.*

Mon pauvre corps est raccourci  
Et j'ai la tête sur l'oreille  
Mais cela me sied à merveille  
Et parmi les torticollis  
Je passe pour des plus jolis.

My poor body is shortened  
And I have my head on my ear  
But it suits me marvelously  
And among the stiff-necked  
I pass for one of the prettiest.

Paul Scarron, 17th century dramatist (cited by Lees, 1985)

**Keywords:** dystonia; torticollis; botulinum toxin; movement disorders; basal ganglia

**Abbreviation:** ICD = idiopathic cervical dystonia

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## Introduction

Idiopathic cervical dystonia (ICD), the most common form of adult-onset focal dystonia (Nutt *et al.*, 1988), is defined as involuntary twisting and turning of the neck caused by abnormal involuntary muscle contractions (Fahn *et al.*, 1987). ICD is also known as 'spasmodic torticollis,' but this term does not stress the dystonic nature of the disease. 'Torticollis' is the physical sign of a twisted neck and may result from various non-dystonic illnesses.

In 1902 Meige wrote 'the morbid condition is not to be found either in the muscles or the nerves but in the mind itself' (Meige and Feindel, 1907), and in the 1960s psychiatrists claimed that the disorder results from castration anxiety [the stiff neck representing an erect phallus (Abse, 1966)] or a symbolic turning away from the world (Cleveland, 1959). The disease is now viewed as a brain abnormality; functional brain imaging, electrophysiological and genetic techniques are used to elucidate the pathogenesis of ICD. The evolution of the concepts used to explain the aetiology of ICD exemplifies our increasing ability to recognize and demonstrate that diverse and sometimes bizarre symptoms may stem from subtle functional abnormalities of the nervous system.

## Clinical features

### *Initial clinical characteristics*

Large clinical series from movement disorder clinics have clarified many clinical features of ICD (Duane, 1988; Chan *et al.*, 1991; Jankovic *et al.*, 1991; Rondot *et al.*, 1991). Most of these studies, in contrast to the older literature (Patterson and Little, 1943; Herz and Glaser, 1949; Meares, 1971; Tibbetts, 1971; Matthews *et al.*, 1978), sought to exclude genetic and symptomatic cases of cervical dystonia (e.g. tardive, stroke, tumour, postencephalitic and childhood-onset). There is general agreement about the typical age at onset, higher incidence in women, characteristics of the dystonic posture and associated neurological abnormalities. However, important questions remain about the prognosis and natural history of the disease in individual patients.

The prevalence of ICD is approximately nine cases per 100 000 population in Rochester, Minn., USA (Nutt *et al.*, 1988). The incidence is sex- and age-related. Women are affected 1.5–1.9 times more often than men (Chan *et al.*, 1991; Jankovic *et al.*, 1991; Rondot *et al.*, 1991). However, the distribution of age at onset does not differ between men and women and roughly conforms to a bell-shaped curve with a peak incidence in the fifth decade. In 70–90% of cases the disease begins between the fourth and sixth decades of life (Duane, 1988; Chan *et al.*, 1991; Jankovic *et al.*, 1991; Rondot *et al.*, 1991).

Symptoms usually begin insidiously, with patients complaining of a 'pulling' or 'drawing' in the neck or an involuntary twisting or jerking of the head. Often, the non-specific symptoms lead to an incorrect diagnosis of arthritis,

cervical radiculopathy, a psychiatric illness, Parkinson's disease or temporal mandibular joint syndrome, and patients may have seen several physicians before they are referred to a movement disorder clinic (Jankovic *et al.*, 1991). When the presenting symptoms have been specifically analysed, sensory symptoms (described variously as pain, pulling or stiffness) or a degree of head rotation or deviation are found in the great majority of patients, with jerking or tremor of the head being distinctly less common complaints (Rivest and Marsden, 1990; Chan *et al.*, 1991; Jankovic *et al.*, 1991).

A wide variety of abnormal head and neck postures may be assumed. Deviations may occur in any single plane or combination of directions in which the head may voluntarily move. Rotational torticollis is a rotation of the chin around the longitudinal axis towards the shoulder; laterocollis is a rotation of the head in the coronal plane, moving the ear towards the shoulder. Anterocollis and retrocollis are rotations of the head in the sagittal plane; anterocollis brings the chin towards the chest and retrocollis elevates the chin and brings the occiput towards the back. There may also be sagittal or lateral deviation of the base of the neck from the midline (Consky and Lang, 1994). Most (Chan *et al.*, 1991; Jankovic *et al.*, 1991), but not all (Jahanshahi *et al.*, 1990), studies have found a combination of these deviations to be most common, occurring in 66–80% of patients. The most common component of complex deviations is rotational torticollis, followed by head tilt, retrocollis and anterocollis. Isolated deviations (e.g. in a single plane) are seen in fewer than one-third of patients. Notably, idiopathic cases of pure anterocollis are extremely uncommon. There is no statistically significant preponderance of right or left deviation (Duane, 1988; Chan *et al.*, 1991; Jankovic *et al.*, 1991; Rondot *et al.*, 1991). The abnormal posture is present >75% of the time in most patients, yet it may change strikingly during the illness, even reversing direction in a few (Chan *et al.*, 1991). Although the term 'spasmodic torticollis' implies head jerking or neck spasms, this feature is absent in 25–33% of patients, a point which has led some (Chan *et al.*, 1991) to suggest abandoning the term for one which stresses the dystonic nature of the disorder (e.g. idiopathic cervical dystonia).

By the time ICD is established, many patients also have dystonia elsewhere or a tremor similar to essential tremor. Although reports of the rates of extracervical dystonia have varied widely in the past, this is likely to be due to differences in the duration of illness and the inclusion of secondary or childhood-onset cases. Extracervical dystonia is found in ~20% of patients (Chan *et al.*, 1991; Jankovic *et al.*, 1991); the jaw (oromandibular), eyelids (blepharospasm), arm/hand (writer's cramp) and trunk (axial) are the most frequently affected parts. A postural or kinetic hand tremor is found in ~25% of patients.

Two types of tremor may affect the head. The tremor is termed 'dystonic' if there is a directional preponderance and it increases in amplitude when the head is deviated away from

the direction of involuntary movement (as in nystagmus). If the tremor is rhythmical, symmetrical and does not change considerably with head movement, it is 'essential.' While most series have not specifically distinguished these tremors, one report of 300 patients found dystonic tremor in 37% of patients and essential tremor in another 30% (Jankovic *et al.*, 1991). It is unclear whether essential tremor in the head or the hand is an additional manifestation of a primarily dystonic disorder or a separate associated movement disorder similar or identical to essential tremor. Although some data suggest that the tremor is part of a single dystonic disorder (Bressman *et al.*, 1996), it will not be possible to make this distinction until the pathogenesis (e.g. genetic characterization) of these disorders is better understood.

Several provocative and palliative factors are characteristic of idiopathic dystonia. Most notable is the use of a sensory 'trick' or *geste antagoniste* to relieve the dystonia by touching the chin, face or head. Other effective manoeuvres include leaning against a high-backed chair, placing something in the mouth or pulling the hair. Early in the illness these tricks are helpful in the great majority of patients, but they tend to lose effectiveness as the disease progresses. Less common palliative factors are relaxation, alcohol and 'morning benefit,' where symptoms are improved for a while after waking. ICD is commonly exacerbated by activity (e.g. walking), fatigue or stress (Consky and Lang, 1994).

### Natural history

Torticollis tends to worsen for 3–5 years, but the duration of progression is highly variable, ranging from 1 month to 18 years (Lowenstein and Aminoff, 1988). The illness culminates in the stabilization of symptoms; there may be a mild improvement phase that precedes stabilization. The dystonia commonly spreads beyond the neck, but does not become generalized. Pain may increase independently of the dystonia. Patients may develop cervical spondylosis with resulting radiculopathy or myelopathy (Waterston *et al.*, 1989). While remissions are not exceptional, they are often not complete or prolonged (Jayne *et al.*, 1984; Friedman and Fahn, 1986; Lowenstein and Aminoff, 1988; Jahanshahi *et al.*, 1990). Many investigators have attempted to address the issues of which clinical characteristics predict remission and what percentage of patients will experience extracervical dystonia, but much of the literature is difficult to interpret because of the absence of clear definitions of remission, heterogeneous patient populations and differing lengths of follow-up. When pure ICD populations are studied and remission is clearly defined as the complete or partial resolution of dystonia unrelated to medication, remission rates of 10–20% are found, and remissions typically occur in the first few years (Friedman and Fahn, 1986; Jahanshahi *et al.*, 1990). A younger age at onset is the only consistent clinical characteristic that appears to predict remission, and remissions tend to be sustained only if they occur after the first 2 years. However, nearly all patients relapse within 5 years, and a cycle of remission and

relapse may recur, although rarely more than three times (Duane, 1988). With respect to extracervical spread, one study, which followed patients for a mean of 7.7 years, documented progression to a segmental pattern of dystonia in one-third of 72 patients who first had isolated cervical dystonia (Jahanshahi *et al.*, 1990). The dystonia typically spread to the face, jaw, arms or trunk.

Disability is common in ICD. Although reports from movement disorder clinics are biased towards severe disease, some degree of disability was found in 99% of 220 patients with ICD, ranging from mild ('subjective feeling of discomfort in social conditions without objective consequences on social life') to severe ('qualitative and quantitative modification of the occupational level with resulting impairment of social life') (Rondot *et al.*, 1991). Many patients will have depression; one report documented depression in 24% of 67 ICD patients (Jahanshahi, 1991). A high incidence of pain distinguishes ICD from all other types of focal dystonia, and contributes significantly to the disability caused by the illness (Comella *et al.*, 1996). Pain is present in ~75% of patients at some point during the illness, and patients usually consider such pain a major source of disability (Lowenstein and Aminoff, 1988; Jahanshahi *et al.*, 1990; Chan *et al.*, 1991; Jankovic *et al.*, 1991). Pain is associated with constant head-turning, greater severity of head-turning and the presence of spasms (Chan *et al.*, 1991). Disability is also caused by task-specific limitations (e.g. inability to drive) and avoidance of social interaction resulting from abnormal posture. Questioning patients about disability and clarifying the contributing factors is crucial for the optimal care of patients with ICD.

### Diagnosis

#### Differential diagnosis

Two issues must be settled to arrive at the diagnosis of ICD. First, it must be confirmed that one is dealing with dystonia, because there are many non-dystonic causes of an abnormal neck posture (Suchowersky and Calne, 1988). Torticollis is a physical sign, not a diagnosis. Also, other hyperkinetic movement disorders may appear dystonic. Secondly, once it is determined that dystonia is present, the history, physical examination and, if necessary, laboratory tests must exclude secondary dystonia.

A variety of lesions involving the CNS, cranial nerves, cervical spine and surrounding soft tissue may cause non-dystonic torticollis. Intra-axial lesions as diverse as posterior fossa tumours, colloid cysts of the third ventricle and lesions of the brainstem and cervical spine (syrinx and tumour) have all been reported to cause torticollis (Kiwak *et al.*, 1983; Suchowersky and Calne, 1988; Cammarota *et al.*, 1995). Patients with intra-axial lesions frequently lack neck pain; the onset may be acute or subacute and additional findings may be noted on examination. Lesions of the cerebellum, caudal brainstem, IVth and rarely the XIth cranial nerves

may cause head tilt. As atlanto-axial rotatory dislocation and C2–3 rotatory dislocation may present as torticollis, a history of head or neck trauma should always be sought. These mechanical types of torticollis are distinguished by persistent abnormal posture during sleep, continuous pain, the absence of typical provocative or palliative factors, and lack of appropriate muscle hypertrophy (Suchowersky and Calne, 1988). Patients with fixed deviations should be suspected of having a mechanical type of torticollis (in laterocollis, 'the early bird listening for the worm'). Sandifer's syndrome manifests as paroxysmal cervical dystonia associated with feeding. Infectious and neoplastic lesions in and about the cervical spine may cause torticollis; appropriate history and physical findings generally make these obvious.

Other types of hyperkinetic movements must be distinguished from dystonia, which is defined as sustained muscle contractions that frequently cause twisting and turning (Fahn *et al.*, 1987). Tics can be prolonged and may transiently twist a body part into a dystonic posture. These movements, initially termed 'tonic tics', are now known as 'dystonic tics' (Meige and Feindel, 1907; Jankovic and Stone, 1991). They are classified primarily as tics rather than dystonia because they can be suppressed voluntarily, are associated with mounting inner tension and are often accompanied by phonations, complex patterned movements and typical clonic tics (Jankovic and Stone, 1991). Myoclonic jerks are brief, shock-like movements and do not cause twisting. Rarely, dystonia may be accompanied by myoclonic jerks (Obeso *et al.*, 1983). EMG analysis of these cases reveals co-contraction of antagonist muscles, and there is no time-locked cortical event. Therefore, these myoclonic jerks are thought to be part of the spectrum of dystonic movements.

Psychogenic dystonia is rare and should be diagnosed with caution (Lesser and Fahn, 1978). In one series of 300 ICD patients (Jankovic *et al.*, 1991), it accounted for ~25% of patients who were initially misdiagnosed. Characteristics that suggest a psychogenic aetiology are abrupt onset, movements that change rapidly or begin as a fixed posture, accompanying bizarre movements (e.g. rhythmical shaking), paroxysmal dystonia and disappearance of movements with distraction. Additional clues are false weakness or sensory findings, multiple somatizations, self-inflicted injuries, obvious psychiatric illness (with the exception of depression) and pending litigation (Fahn and Williams, 1988). The only way to make the diagnosis with relative certainty is by finding persistent disappearance of the movements with psychiatric therapy.

Once it is clear that the abnormal movement is cervical dystonia, a secondary dystonia must be excluded. It is particularly important to exclude early onset Parkinson's disease and other causes of parkinsonism (e.g. progressive supranuclear palsy). The history should focus on additional neurological complaints, head or neck trauma, exposure to drugs that block dopamine receptors, symptoms prior to onset of dystonia, and family history of dystonia. Sudden onset or rapid progression of dystonia or an initial fixed posture

suggest symptomatic dystonia. Apart from dystonia, the only abnormality on examination may be a postural hand tremor similar to essential tremor. Any associated corticospinal, sensory, cerebellar, oculomotor or cortical signs suggest secondary dystonia, which may result from many neurological illnesses (Fahn *et al.*, 1987).

Cervical dystonia may begin within days of head or neck trauma. The relationship of trauma to the pathogenesis of ICD will be discussed below. 'Tardive dystonia' is defined as dystonia occurring within months of exposure to a drug known to block dopamine receptors; it commonly starts in a pattern similar to that of ICD, with a focal or segmental dystonia about the head and neck (Burke *et al.*, 1982; Kang *et al.*, 1986). In addition to neuroleptics, the dyspepsia drugs metoclopramide and clobopride, the antidepressant amoxapine, Triavil or Etrafon (which contain perphenazine) and the calcium channel blockers flunarizine and cinnarizine all block dopamine receptors and may cause a tardive syndrome (Micheli *et al.*, 1987; Ganzini *et al.*, 1993). Finally, Wilson's disease may rarely commence with focal dystonia.

### Laboratory investigation

A secondary cause is only rarely found in otherwise typical ICD; in one study of more than 1000 patients not a single case of Wilson's disease was found and a CNS tumour was uncovered in only two patients (Duane, 1988). Nevertheless, given the variety of CNS lesions which have been associated with cervical dystonia (Kiwak *et al.*, 1983; Lorenzana *et al.*, 1993; Molho and Factor, 1993; Cammarota *et al.*, 1995; Schulze-Bonhage and Ferbert, 1995), MRI of the brain and cervical spine should be considered in all patients. In particular, these studies are recommended in all patients with a fixed painful neck posture. If there is scoliosis, it may be evaluated with plain X-ray so as to document the baseline abnormality. In addition, Wilson's disease should be excluded in all patients under age 50 years by measurement of serum ceruloplasmin and a slit lamp examination. If signs of nervous system disease are not typical of ICD, the evaluation must be expanded to diagnose one of the many causes of symptomatic dystonia, which are reviewed in detail elsewhere (Fahn *et al.*, 1987).

### Pathogenesis

The pathogenesis of ICD is unknown, but there has been great progress in clarifying the genetic abnormality in generalized dystonia, and focal dystonias are now being analysed in the light of this knowledge. There is now clear evidence that a proportion of adult-onset focal dystonia is genetically determined. Trauma has long been recognized to be a frequent finding in patients with ICD, and painful sensory input resulting from trauma may lead to neuronal plasticity within the CNS. Furthermore, physiological studies have implicated the sensory system in the pathogenesis of dystonia.

## Genetics

Three observations support the hypothesis that an abnormal gene is responsible for a proportion of ICD. (i) In families with childhood-onset idiopathic torsion dystonia, for which a genetic basis has been established (Ozelius *et al.*, 1989; Kramer *et al.*, 1990; Warner *et al.*, 1993; Kramer *et al.*, 1994), family members may have focal cervical or segmental dystonia (Zeman *et al.*, 1960). (ii) It has been recognized since 1896 that torticollis may affect siblings (Thompson, 1896), and adult-onset torticollis may affect multiple generations (Gilbert, 1977; Uitti and Maraganore, 1993; Bressman *et al.*, 1996). (iii) A significant percentage of first-degree relatives of patients with focal dystonia have focal dystonia or tremor (Waddy *et al.*, 1991; Defazio *et al.*, 1993; Stojanovic *et al.*, 1995), and in families of patients with ICD the prevalence of focal dystonia is higher than expected (Duane, 1988; Chan *et al.*, 1991; Jankovic *et al.*, 1991; Rondot *et al.*, 1991).

When the family histories of patients with ICD are analysed, cervical dystonia is found in ~10% of first- and second-degree relatives (Duane, 1988; Jankovic *et al.*, 1991), and some form of focal dystonia or essential tremor is found in 26–52% of relatives (Duane, 1988; Jankovic *et al.*, 1991; Rondot *et al.*, 1991). However, the presence of abnormalities in affected relatives tends to be under-reported by patients (Waddy *et al.*, 1991). In three studies (Waddy *et al.*, 1991; Defazio *et al.*, 1993; Stojanovic *et al.*, 1995), the first-degree relatives of patients with any form of adult-onset focal dystonia were examined by investigators. All three studies found evidence of autosomal dominant transmission of focal dystonia with reduced penetrance, but they did not analyse the different types of dystonia separately. It is unclear whether affected family members tend to develop the same type of dystonia exhibited by the probands; this may be true only for torticollis (Stojanovic *et al.*, 1995).

Three large non-Jewish families with adult-onset torticollis have been described. In one, linkage to chromosome 18p has been identified (Leube *et al.*, 1996). There were seven definitely affected and six possibly affected individuals across four generations in this family. The dystonia was largely focal, involving the neck, but there was also an individual with laryngeal involvement. Furthermore, two individuals with torticollis also had segmental dystonia. In another family, among two generations there were five individuals definitely affected (including a pair of monozygotic twins) and five individuals possibly affected with torticollis (Uitti and Maraganore, 1993). The mean age at onset was 35.2 years and dystonia was limited to the neck. Arm tremor was present in one family member with definite dystonia and in two family members with possible dystonia. In the third family (Bressman *et al.*, 1996) the mean age at onset was 30 years, and there were seven definitely affected family members in two generations. In this family six of the definitely affected and seven other family members had arm tremor. Despite a disease duration of up to 44 years, none of the affected

members of any of these families has developed generalized dystonia, and only three individuals have shown progression of cervical dystonia to involve the arm or face. The *DYT1* locus was excluded in the latter two families, so they are not formes frustes of childhood-onset ITD. Clearly, other genes are involved in the pathogenesis of focal dystonia of the cervical muscles.

## Trauma

As early as the mid-1800s, S. Weir Mitchell (1872) recognized that peripheral limb injury could result in abnormal movements, and Gowers (1886–88) described a patient who developed writer's cramp after trauma of the hand. Additionally, in primates frequent simultaneous sensory stimulation of multiple fingers led to difficulty using the hand that was reminiscent of action dystonia (Byl *et al.*, 1996). While there are clear differences in the clinical characteristics of post-traumatic cervical dystonia and ICD, the fact that peripheral trauma can cause dystonia suggests that the sensory system may be important in the pathogenesis of focal dystonia. There is further evidence for this concept in the findings of experiments performed on patients with focal dystonia (Hallett, 1995). A role for trauma in the pathogenesis of focal dystonia may interact with one for genetics, with only genetically predisposed individuals developing dystonia after peripheral injury. Indeed, the minimal intrafamilial correlation for both age of onset and severity of dystonia in familial ITD has been cited as evidence that gene–environment interactions are more important than interactions among genes in explaining the phenotypic variability in that illness (Fletcher *et al.*, 1991).

There are many reports of patients with focal dystonia secondary to trauma (Schott, 1985; Jankovic and Van der Linden, 1988), and two have focused exclusively on torticollis (Truong *et al.*, 1991; Goldman and Ahlskog, 1993), including 11 patients. The injuries were attended by immediate pain followed by the onset of cervical dystonia, with near total neck immobility within a few days. There was usually no early morning relief, rarely was a sensory trick effective and the dystonia often persisted in sleep. The condition persisted unabated during up to 4 years of follow-up and responded poorly to medication and botulinum toxin. Notably, none of these patients reported a family history of dystonia. In the large clinical series previously reviewed, a history of preceding head or neck trauma was found in 9–16% of patients, and usually occurred weeks to months prior to the onset of ICD.

How peripheral trauma produces dystonia is unclear, but the attendant pain may be the important pathogenic factor (Jankovic, 1994). Pain is prominent in nearly all reported cases of post-traumatic dystonia. The role of the basal ganglia in receiving and processing both noxious and non-noxious stimuli has been recognized, as reviewed by Chudler and Dong (1995). Many electrophysiological, metabolic and blood flow studies implicate the basal ganglia in nociception, and

some of these studies have been performed in humans. Using PET, painful thermal stimulation of the hand resulted in increased blood flow in the contralateral putamen and globus pallidus when compared with non-painful thermal stimuli (Jones *et al.*, 1991). A bilateral increase in blood flow within the putamen followed an intradermal injection of capsaicin (Iadarola *et al.*, 1993). The basal ganglia contain some of the highest concentrations of opiate receptors in the CNS, and met- and leu-enkephalin levels have been shown to decrease in the striatum and globus pallidus concomitant with the recuperative limb withdrawal that occurs 1 week after thermal injury (De Ceballos *et al.*, 1986). In addition, the expression of the genes for prodynorphin, c-Fos and c-Jun is altered in the spinal cord and brainstem following painful stimuli (Bullitt, 1989; Herdegen *et al.*, 1991; Lanteri-Minet *et al.*, 1994; Zhang *et al.*, 1994).

Additional data suggest that altered sensory input leads to plasticity of the motor system. The size of motor cortex devoted to the finger musculature of a blind person who reads Braille is larger on the side contralateral to the hand used for reading (Pascual-Leone *et al.*, 1993). In patients who have had a limb amputated, transcranial magnetic stimulation produced larger motor evoked potentials in muscles just proximal to the stump, and motor potentials could be triggered from a larger area of cortex than on the uninvolved side (Cohen *et al.*, 1991). Altered sensory input can cause motor plasticity within minutes; following ischaemic nerve block, transcranial magnetic stimulation produced increased motor evoked potentials in muscles just proximal to the block, and potentials could be produced from a larger area of cortex (Brasil-Neto *et al.*, 1993). The loss of sensory input from myelinated fibres was interpreted as being responsible for provoking the increased excitability and enlarged representation of the motor cortex.

Experiments in patients with focal dystonia have implicated the sensory system in the pathogenesis of dystonia. Two studies in patients with writer's cramp are notable. Using PET, the peak blood flow in response to hand vibration was significantly reduced both in the primary sensory and the supplementary motor cortex compared with normal controls (Tempel and Perlmutter, 1993). Also using hand vibration, dystonia was easily provoked by the 'tonic vibration reflex', and this effect was markedly attenuated by the blockade of muscle spindle afferents (Kaji *et al.*, 1995). These investigators suggest three mechanisms that might explain the increased sensitivity to vibration: lack of normal inhibition of Ia sensory afferents, an 'abnormality' of central pathways, and abnormal muscle spindle responsiveness resulting from overactive gamma spindle efferents. A lack of normal inhibition has been found in other experimental paradigms; ICD patients have an abnormally rapid recovery of the blink reflex and H-reflex recovery curves (Tolosa *et al.*, 1988; Panizza *et al.*, 1990).

These data emphasize that sensory input, painful or otherwise, is received by and alters the physiology of the motor system. Information from large-fibre afferents appears

to be particularly important. However, which physiological changes cause dystonia and specifically how and why they are provoked in particular individuals remains unknown and is the subject of present and future investigations.

### **Other theories**

A long-standing theory of the pathogenesis of ICD is that it results from a primary abnormality of the vestibular system. A large proportion of patients with ICD have asymmetrical vestibular nystagmus in the dark, with the dominant direction opposite that of the torticollis (Bronstein and Rudge, 1986). Furthermore, the vestibulo-ocular reflex is asymmetrical in patients with ICD and fails to correct after treatment with botulinum toxin (Stell *et al.*, 1989). However, the vestibular abnormalities are unlikely to be the primary abnormality. Other forms of focal dystonia (e.g. writer's cramp, blepharospasm) occur with ICD; they have not been associated with a vestibular abnormality. Moreover, dizziness, vertigo and unsteadiness are not features of ICD. Lastly, the vestibular reflex abnormalities are not found in many patients, and tend to occur in patients with a long disease duration (Colebatch *et al.*, 1995). These points suggest that the vestibular abnormalities are secondary to prolonged abnormal head posture.

No consistent pathological or structural abnormalities have been demonstrated in ICD. A pathological study of four patients with idiopathic dystonia found moderate to severe cell loss in the substantia nigra, locus coeruleus, raphe nucleus and pedunculopontine nucleus in a 68-year-old man with a long history of Meige syndrome, but no definite pathological abnormalities were noted in a 50-year-old woman with a 3-year history of torticollis (Zweig *et al.*, 1988). The two other patients in the study had childhood-onset dystonia and likewise had inconsistent findings. Other pathological studies of patients with idiopathic dystonia have not demonstrated any abnormalities (Tarlov, 1970; Zeman, 1970; Hornykiewicz *et al.*, 1986). One report found prolonged MRI T<sub>2</sub> times in the lentiform nucleus of patients with ICD (Schneider *et al.*, 1994). A study using transcranial sonography reported hyperechogenic regions in the lentiform nucleus in patients with idiopathic dystonia; those with tardive dystonia had no such abnormality (Naumann *et al.*, 1996). However, these lesions were also noted in some control patients. Another transcranial sonography study by the same investigators found hyperechogenic lesions in the lentiform nucleus in seven of 10 ICD patients, although only one of the patients displayed an abnormality on MRI (Becker *et al.*, 1997). Assessment of the significance of these findings awaits the demonstration of similar findings by other investigators.

Biochemical studies in adult-onset dystonia have been unrevealing. A patient with adult-onset cranial dystonia was found to have widespread alterations in dopamine, serotonin and noradrenaline, but it was unclear which abnormalities were related to the dystonia (Jankovic *et al.*, 1987). Marked alterations in noradrenaline and serotonin were also noted in

two patients with childhood-onset dystonia (Hornykiewicz *et al.*, 1986). However, treatment with multiple medications (including neuroleptics and diazepam) and a history of bilateral thalamotomies in both patients make interpretation of these findings difficult. Two functional imaging studies have analysed patients with ICD. One, using PET with a D<sub>2</sub> receptor ligand, found a non-significant trend towards increased uptake in the striatum contralateral to clinical findings (Leenders *et al.*, 1993). The other, a single proton emission computed tomography study, also using a D<sub>2</sub> receptor ligand, found significantly greater binding in the striatum contralateral to the direction of head rotation (Hierholzer *et al.*, 1994).

### Treatment

The goals of treatment are to palliate, improve the quality of life and prevent secondary complications. Patients should be reassured that ICD is not dangerous and reminded that cervical dystonia does not become generalized but may spread locally. However, patients should also be told that treatment is symptomatic, not curative. Disability in ICD is caused by many factors (e.g. pain, abnormal posture, functional limitation, social embarrassment, depression) and optimal therapy requires that the physician understand which aspects of the illness are most limiting. It is important to diagnose concomitant depression because it is a major source of disability, will limit therapeutic benefit, and is itself treatable. Secondary complications such as radiculopathy, myelopathy and dysphagia must be recognized and treated.

The evaluation of therapies for ICD is difficult: the abnormal postures, pain and disability are not easy to quantitate, there are spontaneous remissions, and most trials are small and not double-blind placebo-controlled (Lal, 1979). Therefore, no universally accepted treatment protocol exists. However, the treatment of ICD has been revolutionized by chemodenervation with botulinum toxin. Other medications are available, and many patients will require combination therapy. If therapy with botulinum toxin and oral medications fail, surgery may be required.

### Botulinum toxin

The introduction of chemodenervation with botulinum toxin radically changed the prognosis of patients with ICD. Compared with all previous therapies, botulinum toxin benefits the highest percentage of patients in the shortest period of time, has been proven effective in many double-blind placebo-controlled and open trials (Marsden and Fahn, 1994), and has fewer side-effects than pharmacological therapy (Brans *et al.*, 1996). However, important technical questions remain regarding the optimal use of botulinum toxin.

Botulinum toxin is a neurotoxin produced by the gram-positive organism *Clostridium botulinum*; there are seven serotypes of the organism, each of which produces an

antigenically distinct toxin (Simpson, 1981). For ICD, serotype A is most widely used. The use of serotypes B and F is under investigation in patients who have become immunologically resistant to serotype A. The neurotoxins are metalloproteinases that prevent the release of acetylcholine at the neuromuscular junction. Serotype A cleaves synaptosome-associated protein (SNAP-25), a presynaptic membrane protein required for fusion of neurotransmitter-containing vesicles, while serotypes B and F cleave a vesicle-associated membrane protein (VAMP), also known as synaptobrevin (Blasi *et al.*, 1993; Schiavo *et al.*, 1993a, b, 1994).

The preparations of botulinum toxin marketed in the United States (BOTOX), the United Kingdom (Dysport) and Japan (CS-BOT) differ in potency. The standard unit of measure is derived from a mouse assay; one unit of toxin is defined as the amount required to achieve the LD<sub>50</sub>. Theoretically, this should standardize toxin dosages, but in clinical practice one unit of BOTOX is equivalent to approximately three units of Dysport. This is because the mouse assay measures a parameter different from that assessed in clinical use. Efforts are under way to improve standardization by measuring clinically relevant actions of the toxin, for example a 'median paralysis unit' (Pearce *et al.*, 1995).

The most important factor in botulinum toxin administration is the identification of the sites of pain and the muscles responsible for the abnormal posture. A good understanding of the muscles that act on the head and neck is required. The sternocleidomastoid, trapezius, splenius capitis and levator scapulae are most commonly injected. An EMG study of 100 patients found that two or three muscles are most commonly abnormal (Deuschl *et al.*, 1992). Eighty-nine percent of the patients with 'rotating torticollis' (72% of the patients) had involvement of the contralateral sternocleidomastoid and the ipsilateral splenius capitis with or without the additional involvement of the contralateral splenius capitis. Those with laterocollis had ipsilateral sternocleidomastoid, splenius capitis and trapezius involvement, while retrocollis was most often produced by bilateral splenius capitis activity. Complex patterns (8% of the patients) displayed widespread abnormal muscle activity. There is wide variability in the number of muscles injected, the number of injections per muscle, the concentration of botulinum toxin employed and the use of EMG-assisted injections among other technical details. Which technique provides optimal results remains to be determined.

Subsequent to the initial successful double-blind trial (Tsui *et al.*, 1986), many studies confirmed the benefits of botulinum toxin injections for ICD. Two of the largest are representative (Greene *et al.*, 1990; Jankovic *et al.*, 1990). During a 12-week period, 55 patients who had previously failed two trials of medication received either botulinum toxin or placebo in a double-blind fashion, followed by a 4-week open phase when all patients received botulinum toxin. By 6 weeks, 61% of patients showed improvement in head posture (40% moderate or marked) and 39.5% reported reduction of pain. Both measures were significantly improved

compared with controls. During the open phase, those who previously received placebo (and had no appreciable improvement) exhibited a similar response. Overall, 74% of patients improved by the end of the study. A retrospective review of 205 patients treated with botulinum toxin over a 5-year period found improvement in posture in 71% and improvement of pain in 76% of patients. The dramatic improvement in the lives of those treated with botulinum toxin injections is perhaps best illustrated by one controlled study in which four of five patients experiencing the side-effect of severe dysphagia requested repeat injections; the patients 'considered the benefit outweighed the discomfort of the dysphagia' (Blackie and Lees, 1990).

A benefit from botulinum toxin is generally seen within the first week but may rarely be delayed for up to 8 weeks. The benefit lasts for an average of 12 weeks, and most physicians suggest repeating the injections every 3–4 months. The pattern of deviation does not appear to have an effect upon the response, although this point has not been widely studied (Greene *et al.*, 1990; Anderson *et al.*, 1992). Patients continue to benefit from injections and may experience a progressive improvement of dystonia with continued botulinum toxin injections (Jankovic and Schwartz, 1993; Van den Bergh *et al.*, 1995).

Dysphagia, neck weakness and local pain at the injection site are the most commonly reported side-effects, but dizziness, dry mouth, a flu-like syndrome, lethargy, dysphonia and generalized weakness have all been reported. Most studies have reported side-effects in 20–30% of patients per treatment cycle and ~50% of patients at some time during their therapy. However, the frequency of side-effects varies widely, apparently based on the dosage used. Studies employing the highest dosages reported side-effects in nearly 100% of patients (Moore and Blumhardt, 1991), whereas the use of low dosages resulted in a frequency of side-effects in as few as 7% (Van den Bergh *et al.*, 1995).

Pharyngeal weakness (experienced as dysphagia) is a particularly concerning side-effect; it may lead to aspiration, and in a single reported instance it resulted in upper airway obstruction (Borodic *et al.*, 1990). However, dysphagia is generally mild and only rarely requires the institution of a soft diet (Anderson *et al.*, 1992). In one study, 33% of patients receiving their first dose of botulinum toxin experienced dysphagia and a greater number displayed radiographic swallowing abnormalities (Comella *et al.*, 1992). Dysphagia most commonly occurs with injections of the sternocleidomastoid (which overlies the pharyngeal musculature), and it occurs because of local spreading of the toxin (Blackie and Lees, 1990; Borodic *et al.*, 1990). This complication occurs less frequently if multiple small-volume injections are used rather than a single large-volume bolus (Blackie and Lees, 1990; Borodic *et al.*, 1992).

Distant effects of botulinum toxin on neuromuscular transmission have been demonstrated by single-fibre EMG, although there were no clinical symptoms in these patients (Girlanda *et al.*, 1992). In contrast, severe and prolonged

side-effects have been reported in patients with underlying neuromuscular disease (Erbguth *et al.*, 1993; Emmerson, 1994; Mezaki *et al.*, 1996). Distant autonomic effects of botulinum toxin have also been documented (Claus *et al.*, 1995). Although it is conceivable that these autonomic effects may be due to a central effect of botulinum toxin (Habermann, 1974), they are more likely to be a result of action at the postganglionic parasympathetic nerve terminals.

Two groups of patients fail to respond to botulinum toxin. Primary non-responders are patients who do not respond to the first treatment of botulinum toxin. Secondary non-responders are patients who, although initially responsive, subsequently become refractory to injections. Primary non-response results from contractures (long-standing disease), insufficient dosage of botulinum toxin, injection of the incorrect muscles, or some other technical factor (e.g. failure to properly prepare the botulinum toxin). About half of these patients will subsequently benefit from botulinum toxin injections (Poewe and Wissel, 1994). EMG may be required to properly localize the muscles primarily responsible for the dystonic posture in these patients. However, even after these factors are considered some patients will still fail to benefit. This is believed to result from the involvement of inaccessible deep neck musculature, but no studies have specifically analysed these patients.

Secondary failure to respond to botulinum toxin occurs because of a change in the pattern of muscle activity (Gelb *et al.*, 1991) or the development of neutralizing antibodies. These possibilities are easily differentiated; patients who develop neutralizing antibodies do not develop atrophy in injected muscles. The development of neutralizing antibodies is a serious problem because it obliterates any future response to botulinum toxin, although rarely patients who develop antibodies may continue to receive benefit from injections (Hambleton *et al.*, 1992; Zuber *et al.*, 1993). Neutralizing antibodies develop in at least 5–10% of treated patients (Borodic *et al.*, 1996), and antibodies are found in ~33% of non-responding patients (Jankovic and Schwartz, 1991; Jankovic and Schwartz, 1995). Failure to detect antibodies in many patients who lose responsiveness to botulinum toxin is due to a highly specific but insensitive assay (Borodic *et al.*, 1996). It has been suggested that any patient who loses responsiveness to injections and fails to develop atrophy in injected muscles should be assumed to have developed neutralizing antibodies (Greene *et al.*, 1994). A short interval (Zuber *et al.*, 1993; Greene *et al.*, 1994) between treatments (e.g. <3 months) and high doses (Greene *et al.*, 1994; Jankovic and Schwartz, 1995) (>300 units per treatment with BOTOX) are associated with the development of an antibody response.

Clarification of the factors associated with the development of an antibody response is required. For example, it is unknown whether there is a difference in immunogenicity between BOTOX and Dysport. As a consequence of the foregoing data, a recommendation that botulinum toxin injections be given no more frequently than every 3 months

and at a maximum dose of 100 units botulinum toxin (~300 units Dysport) per treatment session has been made (Borodic *et al.*, 1996). However, in our experience 100 units will not benefit most patients with ICD, and we routinely inject 200–250 units per session. If the clinical response remains inadequate adjunctive medications should be used.

### Pharmacological therapy

Medications are generally used as adjuncts to botulinum toxin, although no trial has sought to demonstrate a synergistic effect. Higher dosages and more frequent injections of botulinum toxin are associated with neutralizing antibodies (Greene *et al.*, 1994), so a particular benefit of medications may be to prevent this complication. Most of the information on medication derives from trials on generalized dystonia; few reports have specifically evaluated the efficacy of medication on ICD.

Anticholinergics, benzodiazepines, baclofen, tegretol, tetrabenazine and diphenhydramine are all effective in a percentage of patients (Greene *et al.*, 1988). However, anticholinergics, benzodiazepines and baclofen are the most widely used. Anticholinergics are effective in generalized dystonia and benefit ~40% of patients (Fahn, 1983; Burke *et al.*, 1986). However, reports specifically evaluating anticholinergics in ICD have found them unhelpful (Lang *et al.*, 1982), and they produce more side-effects than botulinum toxin (Brans *et al.*, 1996). Factors that appear to predict a favourable response include younger age (due to toleration of side-effects) and a duration of dystonia of <5 years (Burke *et al.*, 1986). Side-effects may be controlled with cholinomimetic eye drops and pyridostigmine. Benzodiazepines, particularly clonazepam and diazepam, are useful in mild cases of dystonia (Ziegler, 1981). Baclofen is occasionally effective, but has been studied mainly in oromandibular and generalized dystonia (Greene, 1992). Diphenhydramine may be useful in idiopathic truncal dystonia; its antihistamine properties are thought to mediate its antidystonic effect (Truong *et al.*, 1995; van't Groenewout *et al.*, 1995). Use of dopamine receptor-blocking drugs is discouraged because they may cause an irreversible tardive disorder. Clozapine, reported to be beneficial in tardive dystonia (Lieberman *et al.*, 1989; Friedman, 1994; Trugman *et al.*, 1994), has not been extensively studied in ICD (Thiel *et al.*, 1994).

### Surgical therapy

Surgical therapy is only recommended for patients whose dystonia is prolonged, unresponsive to adequate trials of medication and botulinum toxin injections, and associated with significant pain or disability. Since the introduction of botulinum toxin, surgery is rarely required. No controlled trial has proven surgery effective, and a retrospective comparison of the natural history of surgical and medical experience at one hospital found that most medically treated

patients maintained a high level of function, while there were many disabling complications in the surgically treated patients (Tibbetts, 1971).

Peripheral denervation procedures designed to denervate dystonic muscles selectively are the most widely practised surgical procedures. The cervical spinal nerves divide into ventral and dorsal roots. The ventral roots form the cervical and brachial plexuses while the dorsal roots supply the posterior muscles of the head and neck. 'Selective ramisectomy' is a procedure that involves the selective section of dorsal rami of the upper cervical spinal nerves (Davis *et al.*, 1991; Arce and Russo, 1992; Bertrand, 1993; Braun and Richter, 1994). Sparing of the ventral roots leaves the cervical and brachial plexuses intact, decreasing the complications of diaphragmatic paralysis and dysphagia. However, others have reported comparable results with selective sectioning of ventral rootlets (Friedman *et al.*, 1993). Selective denervation procedures are often combined with selective spinal accessory nerve section, anterior rhizotomy or myotomy.

The largest and most recent series is that of Bertrand (1993), who reported the results of 260 patients. Intraoperative EMG was used to identify the muscles involved, and the nerve supply to those muscles was determined by stimulating and anaesthetizing nerve roots. Posterior cervical muscles were denervated by extradural rhizotomy of C1 and C2 and selective ramisectomy of C3 to C6. The sternocleidomastoid was denervated by sectioning branches of the spinal accessory nerve, and the muscle belly was subsequently sectioned. Denervation of the trapezius was avoided for fear of producing shoulder weakness, and was only performed in a second procedure if absolutely necessary. Patients with retrocollis, therefore, underwent bilateral ramisectomy from C1 to C5 without denervation of the trapezius.

Of the 260 patients reported by Bertrand, 88% had an excellent ('no abnormal movements') or very good ('slight residual movements or abnormal posture') result. Only 1% of patients had a poor ('no improvement or worse') result, and the only surgical complication was the development of an abscess in a single patient. Sequelae of the procedure include sensory loss in the distribution of the greater occipital nerve, paraesthesiae, and occasional sudden tic-like pain. Other large series have reported similar results (Arce and Russo, 1992; Braun and Richter, 1994). However, all series suffer from incomplete information about the length and frequency of follow-up, the number of patients seen for follow-up and the method of evaluation. None of the surgical series used formal torticollis rating scales or blinded evaluation (i.e. pre- and postsurgical video assessment). Furthermore, it is difficult to predict which patients are the best candidates for surgery, although there is an impression that those with rotational torticollis or a marked past response to botulinum toxin are most likely to benefit (Braun *et al.*, 1995).

Microvascular decompression involves dissecting the vertebral or posterior inferior cerebellar artery from the spinal

accessory nerve, upper cervical nerve roots or the brainstem; no nerve section is performed (Jho and Jannetta, 1995). Insufficient clinical experience exists to evaluate this procedure. Furthermore, dystonic spasms are rarely limited to the muscles that are innervated by a spinal accessory nerve.

## Conclusion

Much progress has been made in defining the clinical characteristics and symptomatic treatment of ICD. Clinical diagnosis of ICD is now relatively straightforward. However, accurate prediction of the natural history of ICD in individual patients is not possible. Identification of clinical features or laboratory findings that reliably predict the subsequent course would improve the care of ICD patients. Additionally, improved understanding of the factors responsible for immunity to botulinum toxin and the ability to prevent or control this response are needed. Further development of additional strains of botulinum toxin for clinical use and novel treatment strategies based on the use of multiple serotypes would represent a significant advance in the treatment of focal dystonia.

The pathogenesis of ICD remains largely speculative. In fact, although the physiological abnormality in idiopathic dystonia is thought to arise from the basal ganglia, even this basic assumption is open to question (Ikoma *et al.*, 1996). Clearly, identification of the specific mutations in familial torticollis will represent a major advance in our understanding of ICD. Identification of the genetic mutations responsible for focal dystonia will open exciting new avenues of research, such as the production of animal models. Hopefully these research efforts will advance our understanding of the pathogenesis of ICD and lead to improved therapies or a cure for ICD.

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