Primary Torsion Dystonia

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The term primary torsion dystonia describes a group of neurodegenerative disorders characterized by prolonged muscle contractions that cause sustained twisting movements and abnormal postures of affected body parts. Despite early clear descriptions of this disorder, primary torsion dystonia was recognized as a distinct entity very recently, and it was more than half a century before physicians accepted that this seemingly bizarre condition was due to a hereditary brain disease. This article highlights several citations regarding the history of the initial descriptions and the discoveries of the genetic aspects of the disease.

FIRST CLINICAL DESCRIPTIONS

Since its first descriptions in the late 19th century, there has been much debate about the diagnostic clinical entity dystonia and its nosologic classification and etiology. The clear description of the disease entity dates back to 1911, when Hermann Oppenheim, an esteemed Berlin neurologist, became interested in the variation in muscle tone seen in a neurologic syndrome he had encountered in several young boys:

Upon detailed inspection, it becomes obvious that isolated muscles have a tendency to a moderate tonic tension. There might also be a mixture of clonic and tonic phenomena. However, it would be erroneous to interpret this tendency for tonic muscle cramps as a generalized hypertonia. On the contrary, we are surprised to encounter rather a hypotonia upon passive movement of the lower extremities. That is to say that in addition to an increased tonus of some muscles, one finds hypotonia of most of the others.

He further described a “certain clumsiness, especially of the upper extremities, and the movements are neither graceful nor elastic but rather stiff and disjointed.”

He coined the term dystonia musculorum deformans to indicate that “muscle tone was hypotonic at one occasion and in tonic muscle spasm at another, usually, but not exclusively, elicited upon voluntary movements.” In addition to alteration of muscle tone, Oppenheim described additional predominant features of the disease, such as twisted postures associated with the muscle spasms that affect the limbs and trunk, bizarre walking with bending and twisting of the torso, and the progression of symptoms, eventually leading to sustained fixed postural deformities. He also reported, as originally described by Destaaca, that dystonic movements are typically aggravated by voluntary movements. He therefore used a second term for this syndrome, dysbasia lordotica progressiva, emphasizing the progressive nature of the disorder and the abnormal gait with twisted postures of the trunk.

The landmark article by Oppenheim generated controversy, predominantly because he never concisely separated the phenomenon of dystonia from the disease entity he described, so that dual use of the term dystonia in referring to a sign and a syndrome produced nosologic confusion for many years. A second problem resulted from use of the term dystonia musculorum because Oppenheim apparently considered the primary abnormality to be in the muscle.

In their 1911 article, Flatau and Sterling, neurologists from Poland, objected to the term dystonia because they did not regard the varying muscle tone as the clinical hallmark of the disease but rather torsion spasms. They suggested the name progressive torsion spasm:
We cannot feel satisfied with the designation recommended by Oppenheim (Dysbasia Lordotica Progressiva and Dystonia Musculorum Deformans) because in many patients . . . the disease is expressed just as strongly in the upper extremities as in the lower ones, and dysbasia is not the principle symptom. Also, no hypertonia could be detected in our patients. Since the nature of the disease is still unknown to us we should retain its most outstanding characteristic in the designation. In our opinion this consists in the drawing, twisting spasm which is progressive in these affected children, so we select the designation “progressive torsion spasm.”

In retrospect, this definition was more accurate for this form of dystonia, and adoption of the term progressive torsion spasm might have avoided much of the nosologic confusion that followed. However, history has shown that Oppenheim’s term dystonia was prioritized for the disorder, and his name is now eponymously linked to the disease.

Whereas Oppenheim is usually linked to the definition of the disease, Schwalbe is credited with the actual discovery of the condition. In his doctoral thesis from 1908, he first clearly recognized the condition as distinct from previously recognized movement disorders. He also recognized the hereditary nature of the disease, which he observed in a Jewish family. Although isolated cases had been described previously, Schwalbe was the first to describe thoroughly the symptoms of primary torsion dystonia and its genetic predisposition. He considered the disorder to be partly psychiatric, however, calling it tonic crampus syndrome with hysterical symptoms.

The genetic predisposition and the psychiatric genesis of dystonic symptoms generated controversies during the following years. Beyond Oppenheim, Flatau and Sterling also argued for an organic etiology:

The psyche of both patients remained completely undisturbed in the period before the illness and also during its development. . . . The longer we observed the patients, the more deeply we became convinced that we were not dealing here with a functional disease. . . .

How deeply psychological factors have been attributed to dystonic symptoms has been proved by the fact that psychologically based dystonia remains in classifications of dystonias “for the sake of completeness.”

Despite these problems, the term dystonia became widely accepted, and the concept of a primary neurologic disease characterized by prominent dystonia gained acceptance. However, during this initial phase, criteria for the clinical diagnosis of primary torsion dystonia were not clearly established. The term dystonia defined a neurologic disorder and an array of abnormal involuntary movements with a wide range of speed, amplitude, and distribution. Such movements were recognized in different diseases, including Wilson disease, in postencephalitic states, and as sequelae of perinatal brain lesions. This confusion between sign and disease intensified in the 1920s to the point that primary torsion dystonia as a distinct disease entity was rejected from neurologic nosologic classification at the Tenth International Neurological Reunion in Paris, when Wimmer concluded:

Pathology has not been able to bring evidence that torsion dystonia is a disease entity. Dystonia as a syndrome is in no way pathognomonic; it occurs with Wilson’s disease, pseudosclerosis, athetosis, Parkinson’s disease and Huntington’s chorea.

**EMERGENCE OF PRIMARY TORSION DYSTONIA AS A DISTINCT CLINICAL ENTITY**

Fifteen years later, Herz provided a new definition of the disease based on cinematographic studies and electromyographic analysis of dystonic movements (Figure). He finally succeeded in demonstrating...
that primary torsion dystonia exists as an entity of its own. He evaluated 15 cases of his own and undertook an extensive review of more than 100 cases reported by others and finally described the following characteristics:

(a) selective systemic symptoms in the form of dystonic movements and postures, (b) gradual development without recognizable etiological factors at onset.10(p312)

His electrophysiologic measurements had great influence on the precise definition of dystonia, and his frame-by-frame analysis of movements documented the characteristic action-induced twisting movements that typify dystonia. Finally, in 1984, a committee consisting of members of the Scientific Advisory Board of the Dystonia Medical Research Foundation developed the following definition: “dystonia is a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures.”12(p2) This definition is still used. The committee also proposed a classification for all types of dystonia, recommending that there be 3 nosologic schemes: idiopathic or primary torsion dystonia and symptomatic or secondary torsion dystonias.

ETIOLOGY AND GENETIC ASPECTS OF PRIMARY TORSION DYSTONIA

Heredity as the cause of primary dystonia has long been suspected, but early investigators arrived at varying conclusions. Some studies of primary torsion dystonia highlighted 2 important features of the disease: familial occurrence and an ethnic predilection to occur in Jews of eastern European ancestry. Like Schwalbe,6 Flatau and Sterling argued for a hereditary etiology of the disease, alluding to an autosomal recessive inheritance pattern:

We would like to call attention to a peculiar disease which remarkably enough like Tay-Sachs disease has claimed its first victims among Jewish children.5(p605)

However, in the same year (1911), Oppenheim stated in his textbook that “a significant or severe hereditary influence most certainly is not demonstrable.”13(p106) Mendel,13 who created the name torsion dystonia, wrote that although mainly Jewish people are affected, “heredity does not seem to play an essential role . . . because no neurological disease at all had occurred in the ancestors in most cases.”13(p315) Likewise, Herz14 rejected any hereditary contribution to the disease, stating: “My own experience leads me to agree with Mendel that hereditary factors are not traceable in the majority of cases of dystonia.”14(p352) On the other hand, Polish and Russian researchers14,15 consistently proposed dystonia as a definite hereditary disease.

Given that the basic principles of mendelian genetics had been well-established since the beginning of the 19th century, what factors hampered recognition of the genetic contribution to the etiology of primary torsion dystonia? First, the absence of histochemical or pathological changes in association with the disease led to many patients being labeled with a psychological disorder. Second, the influenza epidemics of the 1920s left many cases of secondary dystonias that were confused with the primary dystonia. Finally, the political movements that emerged in Nazi Germany produced an understandable medical reluctance among some investigators to pursue the role of ethnic or familial background in patterns of disease. Herz wrote in his conclusions:

I have not elaborated on the possible prevalence of dystonia in any one group. Similar observations on other diseases of unknown origins (e.g. Tay-Sachs-disease) had to be taken as fact. On the other hand, recent experiences with ‘Rassebiologie’ have been so depressing and grotesque that they do not encourage speculation. . . .11(p352)

Thus, it was not until the late 1960s that the hereditary basis of the disease was recognized. In their hallmark review of clinical, pathological, and genetic aspects of dystonia, Zeman and Dyken16 documented the existence of an autosomal dominant form of the disease. They also described genetic heterogeneity and addressed the concept of the variable expression of dystonia in different affected family members carrying the same defective gene (formes frustes).18 In 1970, Eldridge17 proposed that primary torsion dystonia is inherited as an autosomal recessive trait in Jews and as an autosomal dominant trait in non-Jews. This view was widely accepted for the next 20 years but was rejected in 1984 and in 1990 when reanalysis of Eldridge’s data suggested that the disorder more likely was transmitted exclusively in an autosomal dominant manner but with reduced penetrance.18,39

Ozelius et al20 finally mapped the first primary dystonia locus, DYT1, in 1989 in a large North American family of French-Canadian ancestry with primary torsion dystonia and localized the gene to the 9q32-34 region. Soon after Kramer et al21 found linkage of the disease with 9q markers also in Jewish Ashkenazi families, Ozelius et al22 identified the DYT1 gene (also named Torsin A gene) in 1997 and described a unique 3-base pair deletion in the coding region. This mutation is considered to be responsible for approximately 70% of patients with early-onset primary torsion dystonia but only for a few patients with late-onset primary torsion dystonia. This mutation is more common in the Ashkenazi Jewish population because of a founder mutation, but it has been found in families of diverse ethnic backgrounds. It is now clear that mutations in different genes cause primary torsion dystonia. At least 6 loci have been defined for primary torsion dystonia (DYT1, DYT2, DYT4, DYT6, DYT7, and DYT13), which seems to be associated with a relatively well-defined phenotype but a widely overlapping spectrum of phenotypic expression.

Accepted for Publication: October 19, 2004.

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REFERENCES