Familial Adolescent-Onset Scoliosis and Segmental Dystonia

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ABSTRACT

Idiopathic scoliosis is a common disorder characterized by abnormal curvature of the spine with onset typically in adolescence. Adult-onset primary torsion dystonia (AOPTD) is a focal dystonia with onset in early-middle age consisting of abnormal twisting or directional movements and postures; common phenotypes include cervical dystonia, blepharospasm, and focal hand dystonia. Numerous case reports and case–control studies indicate an association between childhood and adolescent-onset scoliosis and the subsequent development of adult-onset focal dystonia, most commonly cervical or segmental dystonia. In this review we examine the literature linking these two disorders and consider the pathophysiology of their association.

Keywords: adult-onset primary torsion dystonia (AOPTD), segmental dystonia, cervical dystonia, idiopathic scoliosis

INTRODUCTION

Idiopathic scoliosis is a musculoskeletal disorder most commonly arising in the second decade, with a prevalence of up to 4% in 10- to 16-year olds. It is generally defined as curvature of the spine of greater than 10 cm. Although most cases of scoliosis are idiopathic in nature, there is an association with a number of disorders including autoimmune or connective tissue, or local muscle disorders. Scoliosis is also associated with movement disorders including dystonia. Based chiefly on family and twin studies, idiopathic scoliosis is generally considered to be an autosomal-dominant disorder involving multiple genes with variable phenotypic expression and incomplete penetrance.

Dystonia is a common hyperkinetic movement disorder characterized by abnormal twisting or directional movements and postures. Adult-onset primary torsion dystonia (AOPTD) is the commonest subtype and is a focal dystonia with onset after the age of 26 years. Common AOPTD phenotypes include cervical dystonia, blepharospasm, and focal hand dystonia, and segmental forms with contiguous affected body parts most commonly involve the neck with the arm or paraspinal muscles. Despite the apparently high prevalence of sporadic AOPTD, up to a quarter of the individuals have a family member affected by one of the AOPTD phenotypes. An autosomal-dominant pattern of inheritance is seen with markedly reduced penetrance in the region of 12–15%.

Investigation of endophenotypes with the aim of improving thus far unproductive AOPTD genetic studies provides evidence that subclinical sensory abnormalities are present in up to half of the first-degree relatives of sporadic AOPTD patients, supporting the hypothesis that apparently sporadic cases represent the only manifesting carrier of autosomal-dominant AOPTD genes in their family.

Scoliosis and Dystonia: It is well recognized that scoliosis can form part of the phenotype of some of the genetic early-onset dystonias including DTY1 dystonia. In addition, dopa-responsive dystonia may present as kyphoscoliosis causing diagnostic confusion or delay, and scoliosis is a common finding in patients presenting in a more typical manner, forming part of the phenotype in up to two-fifths of patients expressing the GTP cyclohydrolase I gene. In addition, it is not uncommon to encounter scoliosis and other musculoskeletal deformity in patients with established focal or generalized dystonia secondary to the persistent abnormal posture that forms part of their phenomenology.

There is a body of evidence however linking adolescent-onset idiopathic scoliosis with the later development of adult-onset focal dystonias, usually cervical or segmental forms. The aim of this review is to examine the literature regarding the association between scoliosis in childhood/adolescence and subsequent development of adult-onset focal dystonia and to consider the possible pathophysiology.

EVIDENCE FOR AN ASSOCIATION BETWEEN SCOLIOSIS AND ADULT-ONSET FOCAL DYSTONIA

The coexistence of scoliosis and cervical dystonia is well recognized, and as far back as 1991 Jankovic et al. demonstrated a rather striking association in 39% of a cohort of over 300 CD patients. Our group previously published an AOPTD pedigree in which segmental dystonia was associated with
adolescent-onset scoliosis. In that family, four cases of cervical dystonia with brachial dystonia were identified, two of whom had a history of scoliosis preceding onset of their dystonia. In addition, four individuals were found to have scoliosis without dystonia. Postural limb tremor was also present or reportedly present in four individuals (Figure 1). The proband was DYT1 negative and did not respond to a trial of L-dopa. In this family, onset of scoliosis ranged from early childhood to age 15 years and cervical dystonia onset was in the early 50-year range.

The association between cervical dystonia and scoliosis was specifically examined in a case–control study in 2003 by Defazio et al. They compared 72 cervical dystonia patients recruited over a 1-year period to 144 healthy controls and found a statistically significant association on multivariable analysis between scoliosis and CD as opposed to other spinal conditions, with the association surviving correction for age, duration of disease, education level, other spinal disorders, or family history of dystonia.

PATHOPHYSIOLOGY OF THE ASSOCIATION

The occurrence of scoliosis and other skeletal disorders following the onset of AOPTD is not uncommon and can generally be considered to be a secondary feature induced by abnormal posture; onset of scoliosis in these cases is significantly above the expected age range for idiopathic scoliosis.

The phenomenon of scoliosis with subsequent development of cervical or brachial dystonia is not fully understood. One hypothesis is that a genetic predisposition to both conditions exists in these families either coincidentally or because of linkage. There is a strong evidence that AOPTD represents an autosomal-dominant disorder characterized by markedly reduced penetrance in the region of 12–15%. Idiopathic scoliosis is generally accepted to have a genetic component; multifactorial autosomal dominant or X-linked transmission are postulated based numerous families. In addition, genome-wide scanning techniques reveal candidate loci on chromosome 6p, 10q, and 18q. However, the reduced penetrance of both disorders makes linkage analysis difficult, and in addition it is possible that the coexistence of these relatively common genetic disorders in some families is coincidental.

It has been proposed that aberrant sensory input to the sensory cortex resulting from abnormal spinal curvature in scoliosis patients may be instrumental in the development of later cervical or segmental dystonia. Given the evidence that AOPTD is an autosomal-dominant disorder with significantly reduced penetrance, it is unlikely that there is a primary causal link between the presence of scoliosis and the development of focal dystonia in adulthood. Nevertheless, one could argue that scoliosis may function as an environmental factor, triggering the onset of CD in genetically susceptible individuals. It is known that some external triggers are particularly associated with the subsequent development of particular AOPTD phenotypes. For example, neck and trunk trauma are specifically associated with the development of cervical dystonia, and local eye disorders are associated with development of blepharospasm. There is also evidence that some patients develop rapid-onset cervical dystonia with a predilection for laterocollis and lower botulinum toxin sensitivity following neck or shoulder trauma. A recent case–control study concluded that there is no association between preexisting scoliosis and...
the development of blepharospasm. These data fit with the hypothesis that scoliosis may act as an environmental trigger for a specific AOPTD phenotype (cervical and segmental dystonia) in genetically susceptible individuals.

An alternative explanation arises from an interesting paper that recently investigated the association between idiopathic scoliosis and reduced intracortical inhibition (a neurophysiological finding typically associated with cervical and other forms of dystonia). They demonstrated that subjects with idiopathic scoliosis had reduced cortico-cortical inhibition on the side of scoliotic concavity with relatively normal findings contralaterally. It is well documented that the unaffected relatives of patients with AOPTD and other forms of dystonia have a number of detectable sensory and other findings considered to be endophenotypes of abnormal gene carriage, often reflecting subclinical basal ganglia integrative dysfunction.

An important study in this regard by Edwards et al. examined manifesting DYT1 patients, nonmanifesting DYT1 carriers and controls. Reduced intracortical inhibition with reduced cortical silent periods was found in DYT1 carriers, regardless of phenotype expression, which is consistent with the reduced GABAergic activity postulated in dystonia; they felt the findings may be explained by secondary change resulting from a primary basal ganglia disorder. It is intriguing to postulate that subclinical effects of dystonia-related genes may in fact be associated with scoliosis early in the lives of these patients, with some subsequently manifesting AOPTD.

CONCLUSION

The association between early-onset scoliosis and the subsequent development of adult-onset focal dystonia is well described in both case reports and case-control studies examining dystonia risk factors. Although the coexistence of these two relatively common disorders may not be causally linked, there is significant evidence for a pathophysiological association that deserves further attention with the potential to advance our understanding of both disorders.

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REFERENCES