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Editorial

Notochordal alterations in axial skeletal-neural dysraphic disorders

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The article of Saraga-Babic and Saraga, "Role of the notochord in the development of cephalic structures in normal and anencephalic human fetuses", describes abnormalities in the intracranial course of the notochord in cranioschisis with encephaloschisis (anencephaly) and in craniorachischisis with encephalomyeloschisis. Based on the importance of early inductive interactions between the notochord, the nervous tissue, and the axial skeleton, they concluded that such notochordal anomalies could play an important role in the abnormal development of the brain and basichondrocranium which characterize these axial dysraphic disorders. These malformations are commonly referred to as neural tube defects. This terminology emphasizes the secondary but clinically relevant neural defects but ingores the primary paraxial mesoderal insufficiency of these disorders (Morris 1972; Alles and Sulik 1990; Marín-Padilla 1991; Müller and O'Rahilly 1991).

The authors should be congratulated for their detailed study, for collecting the human material, which often is difficult, and for preparing the numerous sections required for the proper reconstruction of the intracranial notochord. However, from various developmental observations, a somewhat different interpretation has emerged about the nature or the notochordal anomalies found in cephalic and caudal (clinical and experimental) axial skeletal-neural dysraphic disorders, a preferred terminology for these malformations (Marín-Padilla 1978, 1979, 1991).

When interpreting these notochordal anomalies some developmental events should be considered. The developing axial cranio-vertebral skeleton goes through an early mesodermal, an intermediate cartilaginous, and a late osseous stage. No obvious notochordal anomalies have been described in the mesodermal stage of these malformations. On the other hand, they become quite prominent during their intermediate cartilaginous stage (the stage studied in the above paper). This apparent developmental paradox could be resolved if these notochordal alterations were to be secondary rather than primary anomalies.

Also, the notochordal anomalies should be assessed judging simultaneously the size, length, width and positional angulation of the axial skeleton (cephalic and/or caudal) in which they are found. When the various notochordal anomalies described (e.g. deviation, bending, duplication, displacement and branching) are reconstructed and correlated with the size and position of the axial skeleton, they all seem to represent different aspects of the same basic anomaly, namely folding within a reduced space. The folding (crowding) of the notochord in experimentally induced (vitamin A, sodium arsenate, clofibrate and retinoid acid) cephalic and/or caudal axial dysraphic disorders corroborates this interpretation. Also, the long cephalic notochord, which bends dorsally behind the sella turcica, found in splotch mice with cranioarchischisis and encephalomyeloschisis, supports this interpretation (personal observation). One could postulate that in these axial dysraphic disorders, the notochord grows normally but that eventually it starts to fold in itself through the primarily shorter segments of the cranial or vertebral axial skeleton. A similar mechanism has been proposed to explain the crowding (often described as overgrowth) of the nervous tissue (cephalic or caudal) overlying the shorter segments of the axial skeleton. A primarily short and small cranial or spinal cavity eventually becomes inadequate to lodge and accommodate the growing neural tissue which is progressively forced to fold within itself overrunning the available space (e.g. exencephaly, the Chiari malformation, meningomyelocele).

In essence, these axial skeletal-neural dysraphic disorders could be caused by a mild modification of the basic body plan of the embryo. The number of paraxial mesodermal cells produced by the rostral end of the primitive streak is temporarily reduced such that the subsequently formed axial skeleton should reflect the time when the reduction occurred, how often it occurred, and the degree of cell reduction. Embryonic development as well as the early inductive interactions between the axial skeleton, notochord, and neural tissue should also proceed normally. However, the affected segments of the

axial skeleton will be smaller and shorter than they would have been under normal conditions. The elevation of the neural folds and consequently their eventual closure should also be compromised by the original reduction of paraxial mesodermal cells. The degree of compromise in the closure of the neural folds will determine the degree and the type of neurological involvement. Accordingly, the neural, notochordal and oro-pharyngeal defects which characterize these dysraphic disorders are considered to be secondary anomalies and the result of developmental re-adjusments to a primarily abnormal axial skeleton.

Recently, a possible role of homeobox genes in the embryogenesis of axial skeletal-neural dysraphic disorders has been postulated (Berry 1992a, b; Redline et al. 1992). Probably, the action of these genes will take place during the gastrulation period of embryonic development. At this time, the basic plans for the formation of the embryonic body and its axis are laid down and, supposedly, the fate, direction, destination, and perhaps the number of paraxial mesodermal cells are being determined by these homeotic genes. A mild and temporary reduction in the number of paraxial mesodermal cells produced could cause this type of axial dysraphic disorders.

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