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CASE REPORT

The etiology of congenital scoliosis: genetic vs. environmental—a report of three monozygotic twin cases

Woojin Cho[1] · **Nicholas Shepard**[2] · **Vincent Arlet**[3]

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Abstract

Purpose To describe the presence of congenital scoliosis in a genetically identical population as it relates to the possible genetic vs. environmental etiologic factors.

Methods The authors describe three cases of congenital scoliosis in monozygotic twins. The first pair includes two 4-year-old girls presenting with mirror curves, one of whom had an associated stage I Chiari malformation. The second pair is a 4-year-old girl who presented with thoracic scoliosis, a T10–11 hemivertebra, and multilevel failure of segmentation in the lumbar spine whose identical sibling is unaffected. The third pair includes a 4-month-old boy with T9 and L4 hemivertebra whose brother is also unaffected.

Results All three cases were managed conservatively with observation and remained asymptomatic throughout the duration of follow-up. There were no associations with extraspinal deformities, although one patient presented with concomitant type I Chiari malformation.

Conclusion The variable presentation of congenital scoliosis in a genetically unique population serves as testament to the complexity associated with its development, likely involving both environmental factors and a genetic predisposition.

Keywords Congenital scoliosis · Monozygotic twins · Chiari malformation · Hemivertebra

Introduction

Congenital scoliosis (CS) is a frequent congenital spinal deformity with an incidence of 0.5–1 per 1000 births [1]. Its natural history in which approximately 25% are non-progressive, 25% are mildly progressive, and 50% necessitate treatment is dependent on the type of anomaly, the site of occurrence, and an individual's overall growth potential [2]. Preventative efforts remain difficult since the etiology of CS is likely multifactorial and poorly understood. Current theory holds that CS results from insults to the developing fetal spine during the 5th–8th week of gestation. Whether this initial insult is genetic, environmental or act in combination remains unclear despite ongoing investigation [3]. Monozygotic twins, though poorly represented in the literature, may provide unique insight into how these factors interact resulting in CS. This report presents three cases of congenital scoliosis in monozygotic twins to add to the limited sample presented in current literature.

Case report

All patients signed the consent forms to agree with reporting their cases, and these cases have never been presented or published in any other journals.

Pair 1

A pair of monozygotic twin girls (A and B) born at 34 weeks presented at age 4 years 9 months after having deformities found incidentally in Brazil. Prenatal and birth history were unremarkable. On examination, mild thoracic curves were noted with an otherwise unremarkable exam (Fig. 1). Twin A's radiographs showed a right T1 hemivertebra and left

✉ Woojin Cho
wcho@montefiore.org

[1] Department of Orthopaedic Surgery, Albert Einstein College of Medicine/Montefiore Medical Center, 3400 Bainbridge Ave 6th Floor, Bronx, NY 10461, USA

[2] NYU Langone Orthopedic Hospital, New York, NY, USA

[3] Department of Orthopaedic Surgery, Pennsylvania Hospital, Philadelphia, PA, USA

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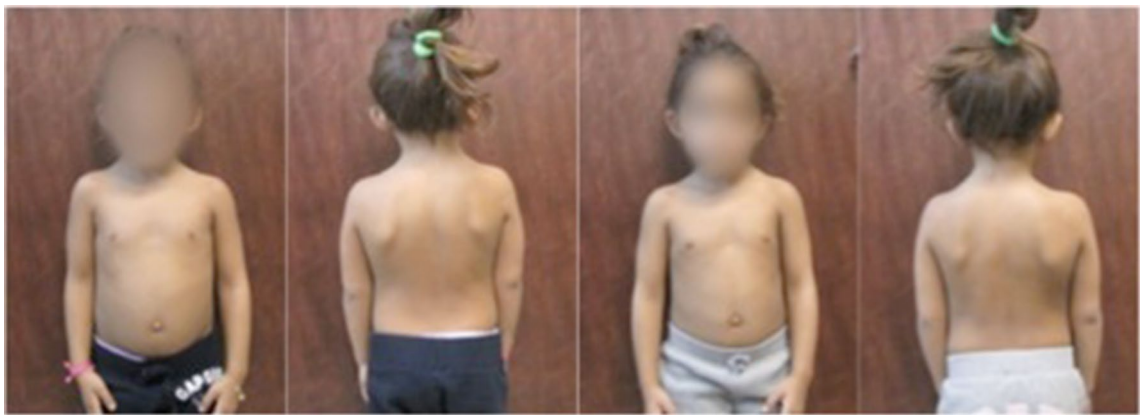

Fig. 1 Clinical examination of twin A (left) and twin B (right) in standing position demonstrated mild thoracic curvature with slight shoulder and scapular asymmetry

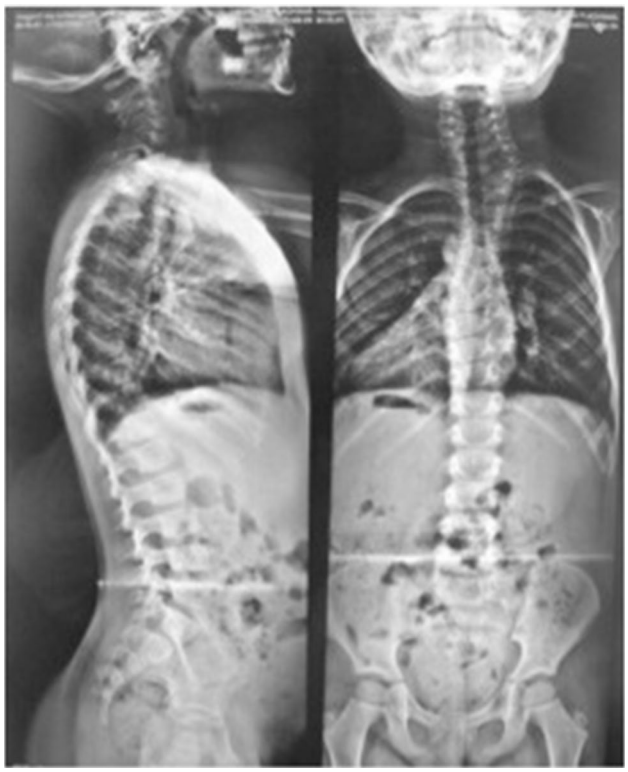

Fig. 2 Plain film X-ray of twin A on presentation demonstrating a right T1 hemivertebra and left T8 hemivertebra, both of which were fused to adjacent vertebra

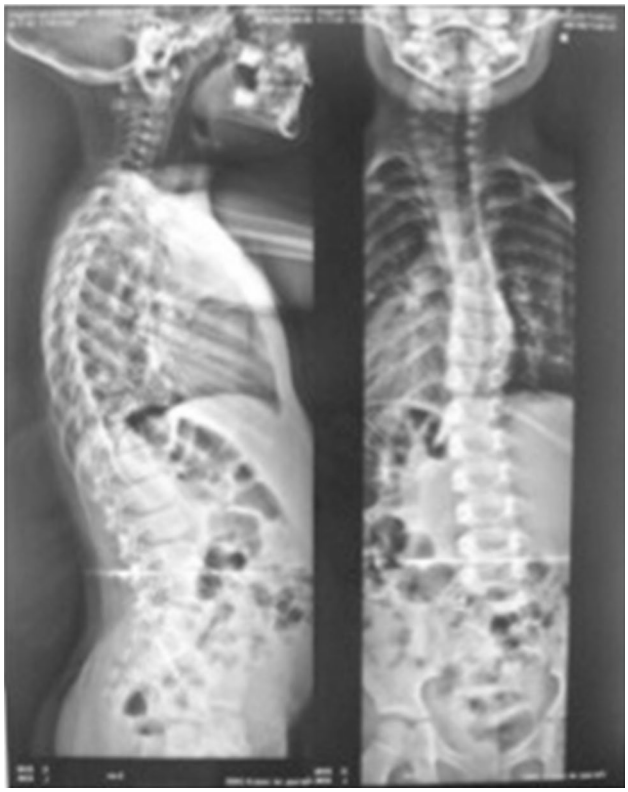

Fig. 3 AP plain film X-ray of twin B demonstrating a left T1 hemivertebra and right T7 hemivertebra, both of which were fused to adjacent vertebra

T8 hemivertebra with metameric shift (Fig. 2). Twin B's radiographs demonstrated a left T1 hemivertebra and right T7 hemivertebra with metameric shift (Fig. 3). In both cases, the hemivertebra were fused to adjacent vertebra but their overall coronal and sagittal balance was normal. Twin B's outside MRI also demonstrated type I Chiari malformation (Fig. 4). After consulting with a pediatric neurosurgeon, the decision was made for careful observation without surgical intervention.

Pair 2

A pair of monozygotic twin girls (A and B) born at 31 weeks presented at age 4 years 10 months after twin

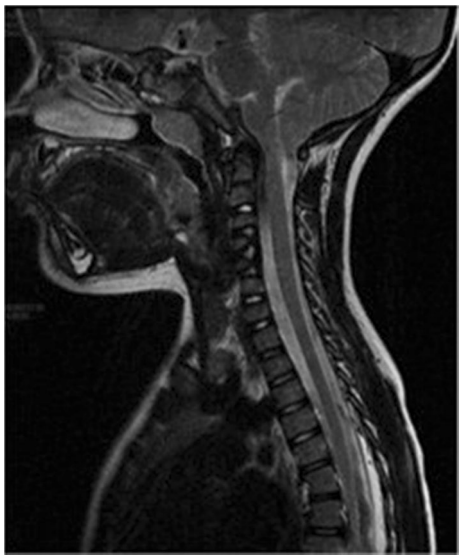

Fig. 4 STIR sagittal MRI of twin B on presentation demonstrating stage I Chiari malformation

Fig. 5 Monozygotic twins (twin A left, twin B right) seen at our clinic. Twin A presented at 4 years of age with congenital scoliosis since age 2 months while twin B was unaffected (normal X-rays not presented)

A was referred for congenital scoliosis noted at age 2 months. On examination, twin A had a left lower thoracic rib hump but her plumbline was midline and her

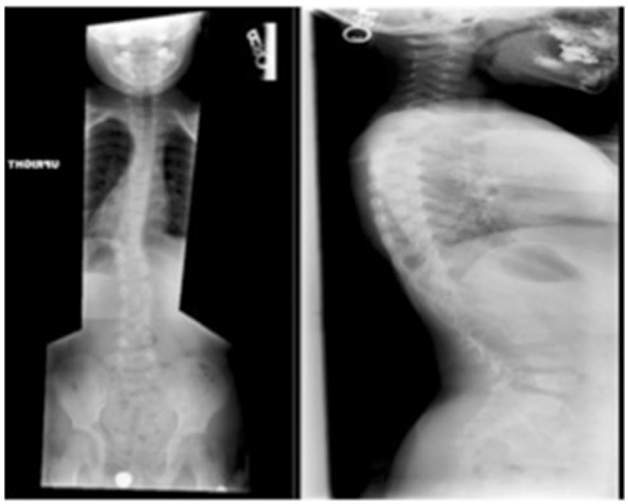

Fig. 6 AP and lateral plain film X-ray of twin A on presentation demonstrating left T10 hemivertebra, left thoracic scoliosis from T9 to T11, and block vertebra with fusion between L1 and L3

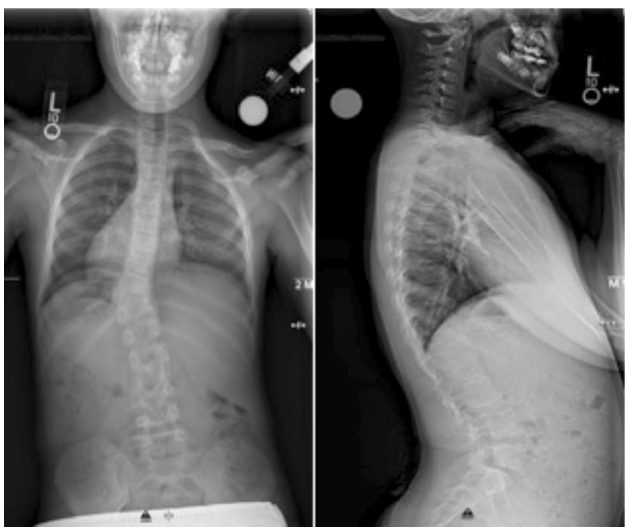

Fig. 7 Five-year follow-up X-rays from twin A demonstrating limited curve progression

exam was otherwise normal (Fig. 5). Scoliosis screening for twin B at the time of presentation was negative. Twin A's radiographs demonstrated a left T10–T11 hemivertebra and block vertebra with failure of segmentation at L1–L3 and mild thoracic scoliosis from T9 to T11 with short segment curve measuring 35° (Fig. 6). The decision was made to follow her curve progression and she was observed over the next 5 years. At her most recent visit the right thoracolumbar hump appeared to be slightly more prominent, but overall she was well aligned and asymptomatic. Repeat imaging did not show worsening of her curve (Fig. 7).

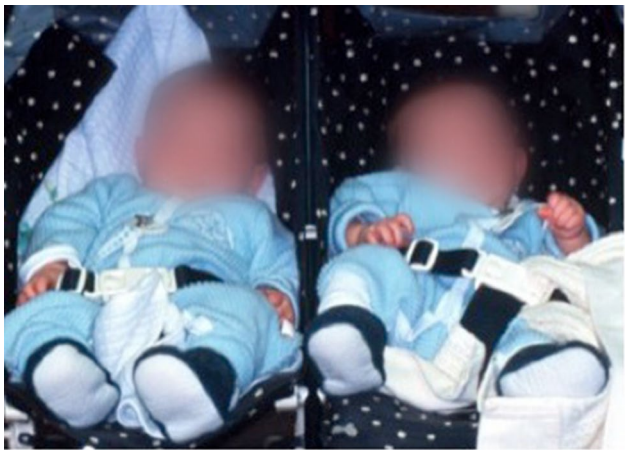

Fig. 8 Monozygotic twin boys (twin A right, twin B left) seen at our clinic. Twin B presented at 4 months with congenital torticollis with visible lumbar hump and sternocleidomastoid contracture. Twin A was normal

Pair 3

A pair of monozygotic twin boys (A and B) presented at age 4 months for congenital torticollis in twin B. On examination, he was found to have a lumbar hump and visible right sternocleidomastoid contracture (Fig. 8). Radiographs demonstrated congenital scoliosis in twin B with left T9 hemivertebra and fused right L4 hemivertebra. His brother (twin A) was unaffected with a normal examination and imaging (Fig. 9). The decision was made for close follow-up with continued monitoring of twin B's curve progression.

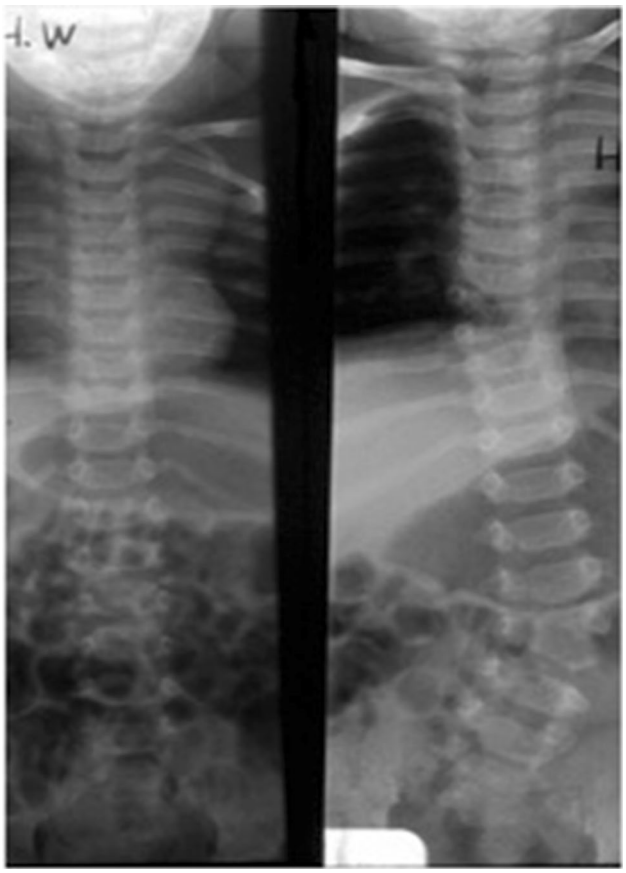

Fig. 9 AP plain film X-rays of twin A (left) and twin B (right) demonstrating left T9 hemivertebra and fused right L4 hemivertebra in the affect twin B and normal spine in unaffected twin A

Discussion

Monozygotic twins provide a unique opportunity to examine environmental and genetic influences in the development of CS. However, this population has been poorly represented in the literature with few reported cases in the setting of CS [4–12]. Here we present three cases of CS in a monozygotic twin population, two of which have a single affected twin indicating the possible role of extrinsic factors and one set of twins who presented with mirror curves suggesting intrinsic, or possibly a combination of genetic and environmental etiologies.

When one monozygotic twin is affected it would seem likely that the underlying mechanism was an extrinsic insult rather than genetic. Various environmental factors including hypoxia [13], carbon monoxide [14, 15], valproic acid [16], hyperthermia [17], maternal alcohol consumption have been associated with CS [18, 19]. Ingalls [13] demonstrated that maternal hypoxia in mice can induce congenital vertebral and rib malformations dependent on the stage of somitogenesis. This was supported with the use of carbon monoxide in pregnant mice that produced the highest incidence of spinal malformations at 9.5 days of gestation, which corresponds with thoracolumbar vertebra development in humans [14, 15]. Similarly, Rivard et al. [20] exposed mice to hypobaric oxygen at the 10th day of gestation and noted lumbar vertebra malformations consistent with those seen in humans. This short-term gestational hypoxia can disrupt FGF signal transduction with downstream effects on the Notch pathway, which is a family of genes critical to the process and coordination of somitogenesis [22, 23]. When disruption occurs it can result in vertebral malformations and errors of somite compartmentalization and segmentation [24].

Hypoxia during early periods of vertebral development also influences the vascularization and appropriate distribution of intersegmental arteries, which are required for resegmentation and early chondrification. When abnormalities occur, normal formation of the vertebral bodies is impaired resulting in deformity [21]. Variability in the distribution of the segmental vasculature may play a large role

in the development of CS following an environmental insult, whereby one twin remains unaffected or two identical twins exhibit phenotypic discordance (e.g., mirroring). If there is sufficient vascular supply to withstand periods of transient hypoxia as described above, the resultant malformations may not materialize. However, if the opposite were true and the intersegmental distribution was such that there was a poor supply at baseline in one twin, the episodes of hypoxia could tip the scale in favor of malformation resulting in a single affected individual. Similarly, if there were variability in the coronal distribution of intersegmental arteries it would be expected that either the right or left side would be more affected. Were this to occur at the same level, a mirror image CS could result. While this may be unlikely, the presence of mirror curves also implicates the possibility of cytogenetic factors in the acquisition of CS.

Conclusion

This report adds three cases to a limited sample of CS in monozygotic twins with one case exhibiting mirror curves and associated intraspinal pathology that is not well represented in current the literature. Two of the cases presented also saw a single twin affected, which serves to demonstrate the effects of both genetic and environmental factors in the development of CS. Further exploration at both the epidemiologic and molecular levels as to how these factors interact and influence early development should be sought to understand the pathogenesis of a common congenital spinal deformity.

Compliance with ethical standards

Conflict of interest None of the authors has any potential conflict of interest.

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