ELSEVIER

CrossMark

The Spine Journal 15 (2015) e19–e23

THE SPINE JOURNAL

Case Report

Long-term clinical and radiological outcomes of Copenhagen syndrome with 19 affected levels: a case report

Francesc Malagelada, MD*, Mathew D. Sewell, FRCS, Amr Fahmy, MBBCh, MSc, MRCS, MD, Alexander Gibson, FRCS

The Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, London HA7 4LP, UK

Received 26 May 2014; revised 7 November 2014; accepted 2 December 2014

Abstract

BACKGROUND CONTEXT: Copenhagen syndrome, or progressive noninfectious anterior vertebral fusion, is a rare disorder of unknown etiology that usually presents with thoracolumbar kyphosis in childhood. There have been no long-term reports on outcome in children with multiple affected levels with longitudinal imaging from infancy to adulthood.

PURPOSE: The purpose of this study was to report the long-term outcome of nonoperative management of a child with Copenhagen syndrome affecting 19 vertebral levels.

STUDY DESIGN: This study is a case report.

METHODS: The study included longitudinal clinical and radiological follow-ups.

RESULTS: A 1-year-old female presented with thoracolumbar kyphosis. Plain radiographs and magnetic resonance imaging demonstrated kyphosis associated with anterior disc space narrowing plus T11–T12 and L2–L3 vertebral end-plate abnormalities. Initial treatment with a plaster jacket followed by brace failed to prevent progressive vertebral involvement and kyphosis during childhood. At skeletal maturity, no further levels became involved, and progression was halted. In total, 19 levels showed anterior fusion.

CONCLUSIONS: This case describes the long-term outcome of nonoperative management for progressive noninfectious anterior vertebral fusion affecting multiple levels. Extensive vertebral involvement does not always require surgical intervention. There is a need for future research on the prognostic indicators for progression and long-term outcome.

Keywords: Spine; Copenhagen syndrome; Kyphosis; Outcome; Progressive noninfectious anterior vertebral fusion; Radiology; Magnetic resonance imaging

Introduction

Progressive noninfectious anterior vertebral fusion (PNAVF) is a rare disorder affecting young children. It is eponymously known as Copenhagen syndrome after a 26-patient case series reported at the University Hospital of Copenhagen [1]. Progressive noninfectious anterior vertebral fusion was first described in 1931 by Mosenthal [2], and it is estimated that there are now 80 reported cases [1]. Some of these cases described in historic non-English articles could possibly have been misdiagnosed as Scheuermann disease.

We performed a systematic review on Pubmed as of October 23, 2014. We searched for the following terms: ''noninfectious vertebral fusion,'' ''spontaneous anterior vertebral fusion,'' ''progressive anterior vertebral fusion,'' and ''Copenhagen disease.'' The search returned 593 articles, and 2 reviewers assessed inclusion criteria based on the accuracy of diagnosis of PNAVF. Sixteen articles were identified that reported the condition including a total of 65 cases of PNAVF [1,3–17].

Progressive noninfectious anterior vertebral fusion presents in early childhood with kyphosis and tends to progress rapidly during adolescence. The deformity is thought

FDA device/drug status: Not applicable.

Author disclosures: ***FM:*** Nothing to disclose. ***MDS:*** Nothing to disclose. ***AF:*** Nothing to disclose. ***AG:*** Nothing to disclose.

* Corresponding author. Department of Paediatric Spinal Deformity, The Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, London HA7 4LP, UK. Tel.: (44) 20-8954-2300.

E-mail address: fmalagelada@gmail.com (F. Malagelada)

http://dx.doi.org/10.1016/j.spinee.2014.12.005

1529-9430/

to stabilize in early adulthood once fusion is complete [1]. The cause remains unknown. It has been postulated that a congenital etiology [1,5] or exposure to prenatal substances like thalidomide might be causative [1,6], although this has never been proven.

The first radiological features that occur shortly after birth include anterior irregularity in involved vertebral body end plates [14]. The anterior part of the disc space narrows and progresses to complete bony ankylosis [6,14]. Posteriorly, the disc is relatively spared in the early stages. Magnetic resonance imaging demonstrates end-plate edema in the anterior discovertebral margins, which precede radiographic changes. Magnetic resonance imaging does not currently provide prognostic information [14].

It is thought that kyphosis is proportional to the number of affected discs and extent of fusion affecting these disc spaces [1]. Treatment involves bracing during childhood to slow progression [1] or surgical correction of deformity [14]. There have been few reports of the syndrome with long-term follow-up, and it is unclear whether more severely affected children, with greater number of affected levels, can be successfully treated by observation and brace treatment. The largest case series involving 26 children described a mean progression of kyphosis from 25.5 to 37.7 over a mean of 13.3 years. Nine of these children were treated by brace alone, of whom six demonstrated improvement in kyphotic alignment [1]. Most case studies report outcome in children with less than 5 affected levels, and we could find no reports involving children with more than 11 affected levels. This case reports outcome of a child with 19 affected levels treated nonoperatively over 20 years.

Case report

A 1-year-old female presented with thoracolumbar kyphosis that had been noticed by the parents. History included hypotonia and mild motor developmental delay. There was no family history of spinal deformity, and obstetric history was unremarkable. On examination, there was a thoracolumbar kyphosis with the evidence of mild generalized hypotonia. Local ethical approval was obtained, and the study was performed following the Declaration of Helsinki principles with consent obtained from the study subject.

Radiographs demonstrated anterior narrowing at the T11–T12 and L2–L3 disc spaces anteriorly with a kyphosis measuring 62° (Fig. 1, Left). Magnetic resonance imaging showed anterior disc height loss at these levels with high signal intensity at multiple end-plate levels, thought to represent normal physeal appearances at this age (Fig. 1, Right). Nonoperative management was started with four serial plaster jackets changed every 10 weeks, followed by a thoracolumbar-sacral orthosis worn for 23 hours a day.

During subsequent follow-up with brace treatment, the child remained asymptomatic, and the degree of kyphosis decreased to 54°. Between the ages of 10 to 12 years, despite bracing, the deformity started to progress with further levels becoming involved. Radiographs at the age of 12 years showed anterior fusion at multiple levels extending between T9–L1 and L2–L5. The kyphotic deformity had increased to 76° (Fig. 2, Left). Magnetic resonance imaging confirmed solid fusion and showed anterior disc narrowing between these levels with evidence of fatty marrow replacement in several vertebrae. The fusion had also involved the posterior elements at several levels (Fig. 2, Right).

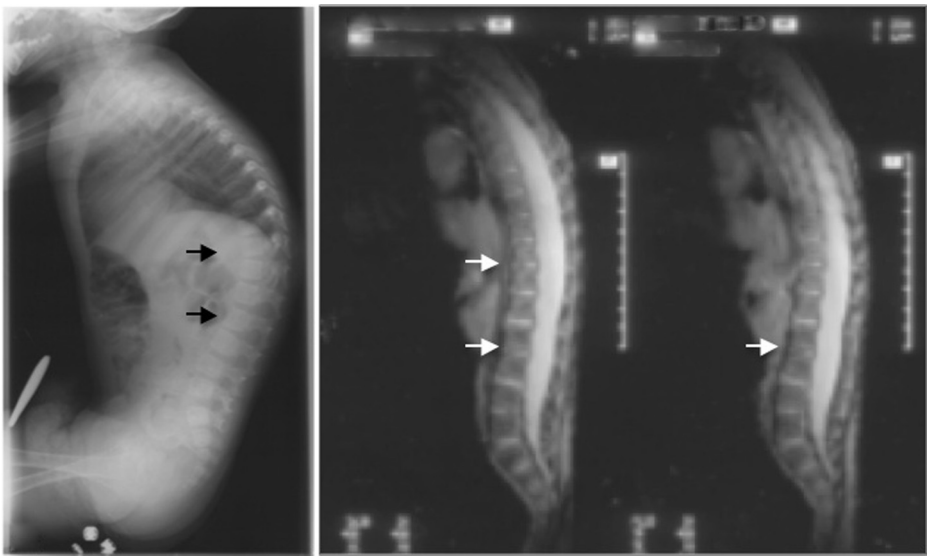

Fig. 1. (Left) Lateral whole spine radiograph at 12 months of age, demonstrating loss of anterior disc space height and end-plate irregularity at the T11–T12 and L2–L3 levels (black arrows). (Right) Sagittal short tau inversion recovery magnetic resonance imaging at 12 months of age of the thoracolumbar spine showing symmetrical disc space narrowing (white arrows). The high signal intensity horizontally at multiple end-plate levels was considered a normal physeal appearance at this age.

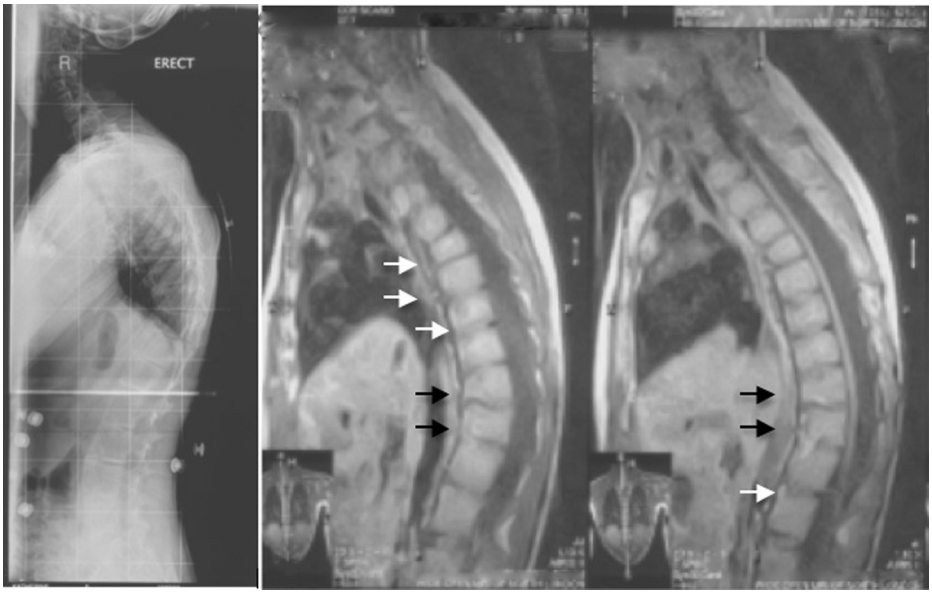

Fig. 2. (Left) Lateral whole spine radiograph at 12 years of age during brace treatment, showing anterior fusion at multiple levels. (Right) Sagittal T1 magnetic resonance imaging of the thoracolumbar spine. There is a solid fusion at the anterior disc at T10–T11 and T11–T12 (black arrows) and multilevel anterior disc space obliteration (white arrows). The discovertebral anterior corner signal intensity changes at the anterior fused bars likely represent fatty marrow changes.

Thoracolumbar-sacral orthosis bracing was discontinued at the age of 15 years once skeletal maturity was reached and the curve had radiographically stabilized (Fig. 3). The patient was reviewed annually until the age of 21 years, during which time no further radiological curve progression was identified (Fig. 4). At the time of the last follow-up, the patient remained asymptomatic with a kyphotic deformity measuring 76°. Visual analog pain score was 0, Oswestry disability score was 6 [18], and the Short-Form 12 questionnaire showed a physical component score of 52.5 and mental component score of 46.5 [19].

Discussion

This case describes the outcome of nonoperative treatment for a multilevel form of PNAVF with long-term follow-up. The child was followed from age 1 to 21 years, and the case demonstrates that successful long-term outcome is achievable with nonoperative brace treatment despite multiple levels being affected and a progressive deformity becoming apparent around the time of the adolescent growth spurt. It is unclear whether brace treatment can prevent deformity progression; however, it can be used successfully to guide spinal growth until skeletal maturity is reached.

The largest series from the University Hospital of Copenhagen [1] including 26 patients found that the majority had only one affected level (10 of 26 patients), and no patients had more than 6 affected levels. Our review of the literature identifies only 1 case report with more than 10 affected levels [12]. This case described a balanced t(10;20) (p11;p13) chromosomal translocation in a child with radioulnar synostosis, exostosis, short and broad clavicles, and 11 affected PNAVF levels. The child in the present study presents as a case of isolated PNAVF without associated genetic abnormality. Only a finding of hypotonia was present from early infancy that resolved with age. No genetic investigations were performed, despite specialist consultation, and the presence of any chromosomic alterations remains unknown.

The location of the fused vertebrae is usually in the thoracolumbar region; cervical spine involvement is rare [1]. Al Kaissi et al. [13] described a child with split spinal cord and situs inversus visceralis with cervical involvement limited to fusion of the lateral masses of the axis with C3. Farrior et al. [10] reported a case involving fusion of three cervical levels in a child with associated syndromic abnormalities including other intraspinal abnormalities. In both cases, the presence of PNAVF was found to be part of an underlying syndrome. The case we present is unique in that cervical involvement was not associated with other spinal malformations. There are a wide variety of presentations of PNAVF that can be broadly divided into isolated cases where vertebral fusion is the only malformation or those with PNAVF as part of an underlying syndrome. Some authors have suggested that this latter presentation may be coincidental [14].

Previous reports have tended to describe the condition and not the detail treatment or outcome. Hughes and Saifuddin [14] reported radiological features of three cases and reported one was treated nonoperatively with plaster jacket and bracing, whereas the other two underwent spinal surgery consisting of anterior release and posterior instrumentation.

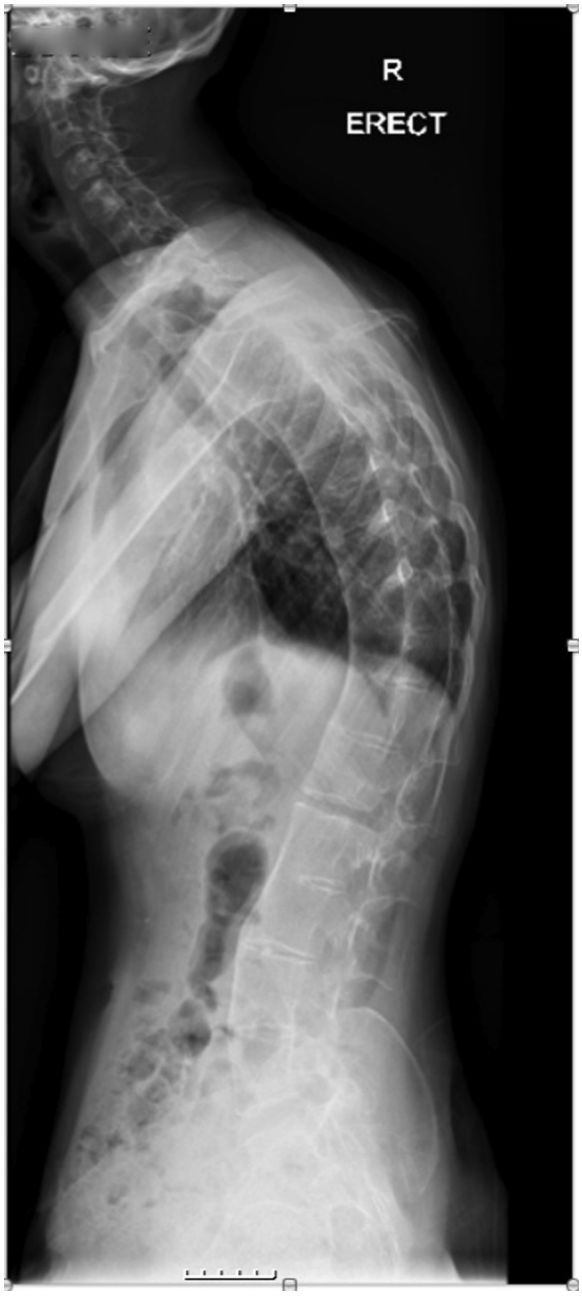

Fig. 3. Lateral whole spine radiograph at 16 years of age showing mature anterior fusion across 19 levels of the cervicothoracolumbar spine. The C1–C2, C3–C5, and C7–T1 levels are the only unaffected levels.

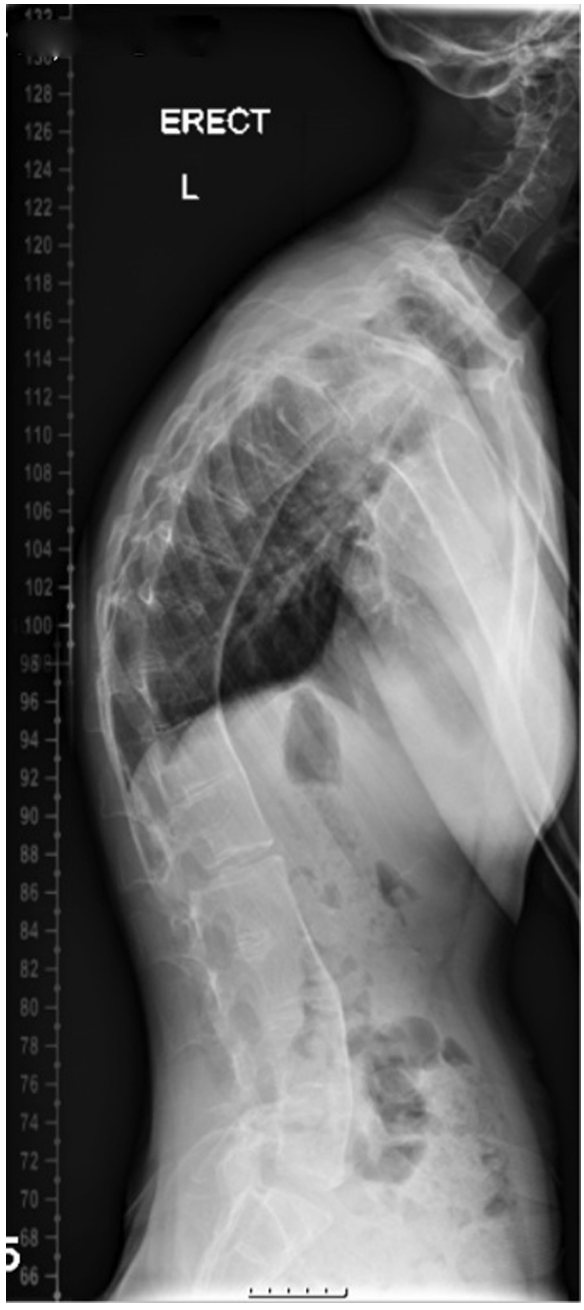

Fig. 4. Lateral whole spine radiograph at 21 years showing kyphotic deformity of 76°.

Similarly, Cebulski et al. [17] focused on radiological findings of the disorder with treatment descriptions limited to physiotherapy and monitoring. In the Copenhagen series, none of the 26 patients were operated on, 9 were treated by spinal bracing, and 15 underwent observation alone [1]. The authors reported an improvement in kyphosis in three patients who underwent spinal bracing. Limited information was provided for type, duration, or frequency of bracing [1].

Previous reports have postulated that progression of kyphosis is related to number of vertebrae involved and extent of disc space fusion [1]. This case would suggest that other factors are involved in the rate of progression. Treatment should be individualized, with brace treatment providing a good early option for children, and surgical intervention reserved for those with marked progression or failure of nonoperative treatment.

Plain radiographs are sensitive to diagnose the features of PNAVF from an early disease stage, with some suggesting these features appear as early as 4 days of age [1]. Magnetic resonance imaging can show end-plate edema and fatty marrow changes within the anterior vertebral

body that are not visible on plain radiographs. Magnetic resonance imaging changes may also precede radiographic changes and can be used as an early imaging modality alongside radiography for the diagnosis of PNAVF, which may easily be misdiagnosed as Scheuermann kyphosis [14].

This is a case report with inherent limitations. No histologic or genetic investigations were performed that may have allowed for better characterization of the condition. The condition was not followed into the elderly stages of life to see how the disease evolved. Future studies should follow cohorts treated by different modalities to assess outcome over long periods.

There is a lack of information to advise on many aspects of PNAVF including etiology, natural history, prognosis, effectiveness of bracing and surgical interventions, details of treatment implementation, and guidelines for clinicians. Treatment should be individualized with close monitoring for progression, with surgical intervention reserved for only those cases where marked progression of the deformity is demonstrated. It may be that these patients need to be monitored and followed similar to those with idiopathic scoliosis [20,21].

Conclusions

Even in multilevel PNAVF, a good long-term outcome is possible with nonoperative management. Closed monitoring and individualized patient management are highlighted, as not all patients will require surgical intervention.

Acknowledgment

The authors would like to thank Ms Gayle D'Souza for her assistance during the preparation of the study.

References

[1] Andersen J, Rostgaard-Christensen E. Progressive noninfectious anterior vertebral fusion. J Bone Joint Surg Br 1991;73:859–62.
[2] Mosenthal. Angeborene kyphose. Z Orthop Chir 1931;53:111–3.
[3] Knutsson F. Fusion of vertebrae following non-infectious disturbance in the zone of growth. Acta Radiol 1949;32:404–6.
[4] Butler RW. Spontaneous anterior fusion of vertebral bodies. J Bone Joint Surg Br 1971;53:230–5.
[5] Kharrat K, Dubousset J. Progressive anterior vertebral fusion in children (author's transl). (in French). Rev Chir Orthop Reparatrice Appar Mot 1980;66:485–92.
[6] Smith JR, Martin IR, Shaw DG, Robinson RO. Progressive non-infectious anterior vertebral fusion. Skeletal Radiol 1986;15:599–604.
[7] Décarie JC, Babyn PS. Progressive noninfectious anterior vertebral fusion: MRI findings and association with a lipoma of the filum terminale in a 5-year-old girl. Pediatr Radiol 1993;23:12–4.
[8] Fryns JP, Fabry G, Remans J, Colla P. Progressive anterior vertebral body fusion, overgrowth and distinct craniofacial appearance. Genet Couns 1993;4:235–7.
[9] Meurisse F, Irani MJ, Davies RJ. MRI of Copenhagen's disease in an adult. Clin Radiol 2001;56:335–7.
[10] Farrior JH, Weaver DD, Kling TF, Klatte E. Progressive vertebral fusion of unknown etiology: a case report. Am J Med Genet 2002;112:221–7.
[11] Stoker D. Progressive non-infectious anterior vertebral fusion ('Copenhagen disease'). Clin Radiol 2002;57:76.
[12] Philip N, Colleaux L, Sigaudy S, Attié-Bitach T, Missirian C, Moncla A, et al. Unusual phenotype with progressive vertebral fusion in a girl with an apparently balanced t(10;20) (p11;p13) translocation. Am J Med Genet A 2005;134A:39–44.
[13] Al Kaissi A, Chehida FB, Ghachem MB, Grill F, Klaushofer K. Progressive non-infectious anterior vertebral fusion, split cord malformation and situs inversus visceralis. BMC Musculoskelet Disord 2006;7:94.
[14] Hughes RJ, Saifuddin A. Progressive non-infectious anterior vertebral fusion (Copenhagen Syndrome) in three children: features on radiographs and MR imaging. Skeletal Radiol 2006;35:397–401.
[15] Al Kaissi A, Grill F, Alexander K, Varga F, Klaushofer K. Progressive noninfectious anterior vertebral fusion in a girl with axial mesodermal dysplasia spectrum. Clin Dysmorphol 2008;17:65–8.
[16] Rocha Oliveira PC, de Deus Leopoldino D. Progressive noninfectious anterior vertebral fusion. Pediatr Radiol 2010;40(1 Suppl):S169.
[17] Cebulski A, Nectoux E, Bigot J, Cagneaux M, Mézel A, Fron D, et al. Progressive anterior vertebral fusion: a report of three cases. Diagn Inerv Imaging 2012;93:53–6.
[18] Fairbank JCT, Pysent PB. The Oswestry disability index. Spine 2000;22:2940–53.
[19] Jenkinson C, Layte R. Development and testing of the UK SF-12 (short form health survey). J Health Serv Res Policy 1997;2:14–8.
[20] Zaina F, De Mauroy JC, Grivas T, Hresko MT, Kotwizki T, Maruyama T, et al. Bracing for scoliosis in 2014: state of the art. Eur J Phys Rehabil Med 2014;50:93–110.
[21] Weinstein SL, Dolan LA, Wright JG, Dobbs MB. Effects of bracing in adolescents with idiopathic scoliosis. N Engl J Med 2013;369:1512–21.