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A neurophysiological and genetic assessment of a case of rapidly progressive scoliosis

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Abstract

Scoliosis is a three-dimensional spinal deformity characterized by a lateral deviation of at least 10° Cobb, categorized into idiopathic and non-idiopathic forms, caused by identifiable factors like congenital abnormalities, neuromuscular conditions, or genetic syndromes. This case report discusses a 15-year-old girl with growth delay and Growth Hormone (GH) deficiency who experienced rapid scoliosis progression. Initial evaluations were normal, and Electroencephalography (EEG) showed nonspecific alterations, but further assessment revealed a MYH3 gene variant associated with scoliosis, short stature, and distinct facial features. Treatment with a Lyon ARTbrace and tailored exercises stopped curve progression. This case highlights the need for thorough evaluations in atypical AIS cases to uncover potential causes.

Key Words: rehabilitation; adolescent idiopathic scoliosis; electroencephalography; GH deficiency; MYH3 gene.

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Scoliosis is a three-dimensional spinal deformity that deviates from its vertical alignment. Diagnosis typically involves identifying a lateral deviation of at least 10° on a posterior-anterior radiograph, coupled with vertebral rotation.[1] On the one hand, Adolescent Idiopathic Scoliosis (AIS) accounts for up to 80% of cases, typically affecting adolescents and having an unclear pathogenesis. On the other hand, non-idiopathic scoliosis refers to spinal curvature resulting from identifiable causes rather than occurring without a known cause. These causes could include congenital vertebral abnormalities, neuromuscular conditions like cerebral palsy or Duchenne muscular dystrophy, and genetic syndromes such as Marfan syndrome and neurofibromatosis. Additionally, scoliosis can arise due to secondary reasons like spinal cord abnormalities, tumors (both intraspinal and extraspinal), and infections. Non-idiopathic scoliosis should be early recognized as it represents a challenge to the physician due to the possibility of curve progression, with the risk of complications such as pain and pulmonary insufficiency.[2] Generally, recognizing a case of non-idiopathic scoliosis is straightforward due to its association with identifiable underlying conditions. Nevertheless, sometimes the diagnosis can be more complex.

We report the case of a 15-year-old female patient who was previously being monitored for growth delay and Growth Hormone (GH) deficiency. She exhibited a notable and unanticipated advancement of her scoliosis.

The patient was born at 39 weeks with a birth weight of 2350 g (2nd percentile) and a length of 45 cm (1st percentile). Despite steady growth, she remained below the 3rd percentile. At age 9, she underwent her first endocrinological evaluation, revealing normal IGF1 levels, a healthy pituitary-thyroid axis, negative celiac disease screening, and normal biochemical profiles. Based on clinical suspicion, genetic testing for Silver-Russell syndrome was performed, but the results were negative. The administration of GH therapy began in late June 2020, resulting in an improvement in growth velocity and a slight increase in stature.

Despite regular monitoring, minimal trunk asymmetries were observed, with no evidence of a hump, even with a family history of severe AIS in the patient's mother and grandmother. Unexpectedly, at the July 2023 evaluation, significant trunk asymmetries were noted, including a

prominent 30 mm right rib hump. X-rays revealed a right thoracic scoliosis with a Cobb angle of 45° and a left lumbar countercurve of 45° (Figure 1A), with a Risser sign of 1, indicating incomplete skeletal maturity. At the time of the examination, the patient had not yet reached menarche.
Given the rapid progression of the curve, additional evaluations were warranted to investigate a potential underlying cause for its accelerated worsening. Electroencephalographic (EEG) data were acquired from 64 channels at a sampling frequency of 500 Hz and referenced to Cpz (ANT Neuro, Enschede, The Netherlands). A 1-min EEG resting state recording of quiet upright standing was acquired first with eyes closed and then with eyes closed on the floor and on a foam support.
The data were processed in Matlab (MathWorks, Natick, MA, Usa) using personalized scripts based on EEGLAB toolbox. The EEG recordings were band-pass filtered from 1 to 40 Hz (the optimal Chebyshev finite impulse response filters were designed using Parks–McClellan algorithm, the order was customized to minimize the error in the pass and stop bands). Noisy channels were identified by visual inspection and interpolated using the nearest-neighbor spline method. Eyes movements and cardiac activity were removed using independent component analysis and data were re-referenced to the average reference. The fast Fourier transform was applied to non–overlapping epochs of 2 s and then averaged across epochs. The recordings were Hanning windowed to control for spectral leakage. Power spectra were estimated for all frequencies between 1 and 40 Hz, then the relative power (%) was calculated by dividing the power of each frequency bands (delta [1–4] Hz, theta [4.5–7.5] Hz, alpha [8–12] Hz, and beta [13–30] Hz) with the total power of [1–30] Hz.
An increase of theta power in fronto-central electrodes was observed when the subject was standing with eyes closed on the foam. The alpha power was localized not only in the occipital electrodes but also in the central electrodes over the sensorimotor areas (Figure 1D).
In addition to the neurophysiological assessment, the patient and her parents underwent whole-exome sequencing to further investigate a potential genetic component, despite initial analysis suggesting its exclusion. This further analysis revealed rare variants, including a heterozygous p.Arg109His variant in the MYH3 gene (OMIM 160720).
All methods were conducted in accordance with the guidelines of the 2008 Helsinki Declaration. Ethical approval was obtained in April 2023 (n. 5627/AO/22). Written informed consent was provided by both the subjects and their legal guardians.
Given the severity of the AIS, the medical team presented the possibility of a surgical solution to the patient and her parents. However, they declined.
The patient was prescribed a Lyon ARTbrace (an asymmetrical, rigid, torsion brace) to be worn full-time and was strongly encouraged to participate in a tailored rehabilitation program.[3]
After 8 months of conservative treatment with brace wearing and tailored exercises, the scoliosis showed a cessation of progression, with a right thoracic rib hump measuring 16 mm on clinical evaluation. On the in-brace X-ray, a notable correction by the orthosis was observed (Fig. 1C); on the out-of-brace X-ray, the thoracic curve was measured at 40°, while the lumbar curve was 34° (Figure 1B).
In the case we presented, an underlying cause for the scoliosis was found after extensive genetic investigations. What initially appeared to be idiopathic scoliosis was eventually revealed, due to a sudden progression, to be linked to a rare genetic variant.
The patient had been undergoing GH treatment for three years prior to the progression of the curve. Although GH treatment in children with short stature has been shown to increase growth velocity, there is currently no evidence to suggest an association between GH treatment and the development or exacerbation of AIS.[4] However, a study involving patients with idiopathic short stature who underwent GH treatment found that 3.7% developed new-onset scoliosis during treatment, while scoliosis progressed in 16.4% of cases.[5]
The results of the EEG evaluations indicated that the theta relative power was elevated over the fronto-central electrodes during the performance of the standing task on the foam with eyes closed. This observation is consistent with the hypothesis that the demands on postural control and sensory processing are increased in patients with scoliosis.[6] Furthermore, alpha power was observed in both occipital and central electrodes over the sensorimotor regions, suggesting likely increased motor control to compensate for altered body perception. In the past, EEG evaluations have primarily been conducted on patients with idiopathic scoliosis,[7] making our case the first to investigate this rare genetic variant from an EEG perspective during balance maintenance tasks.
Genetic investigation identified a rare variant, which is of maternal origin. The MYH3 gene encodes an embryonic heavy chain myosin that is essential for sarcomere assembly in skeletal and cardiac muscle cells.[8] A recent study found 17 individuals with previously unreported MYH3 variants who had scoliosis, short stature, and distinct facial features.[9] These characteristics were subsequently observed not only in our patient but also in her mother and grandmother.
This case report illustrates that when patients exhibit trunk asymmetries or AIS with rapid progression, and there is clinical suspicion of a non-idiopathic etiology, further evaluations are warranted. Identifying the precise cause of scoliosis in such cases is important, as it can significantly influence treatment decisions and outcomes. The patient history collection should guide in selecting which investigations should be performed to explore possible causes of non-idiopathic scoliosis.[10] Advanced diagnostic tools, such as genetic testing and neurophysiological assessments, can uncover underlying conditions that might not be apparent through initial evaluations. Our approach identified a rare genetic variant as a potential cause, and highlighted increased motor and sensory processing, even in simple tasks, as possible effects of scoliosis. These findings may have implications for longitudinal patient monitoring and early intervention strategies in assessing familial predisposition to develop scoliosis.

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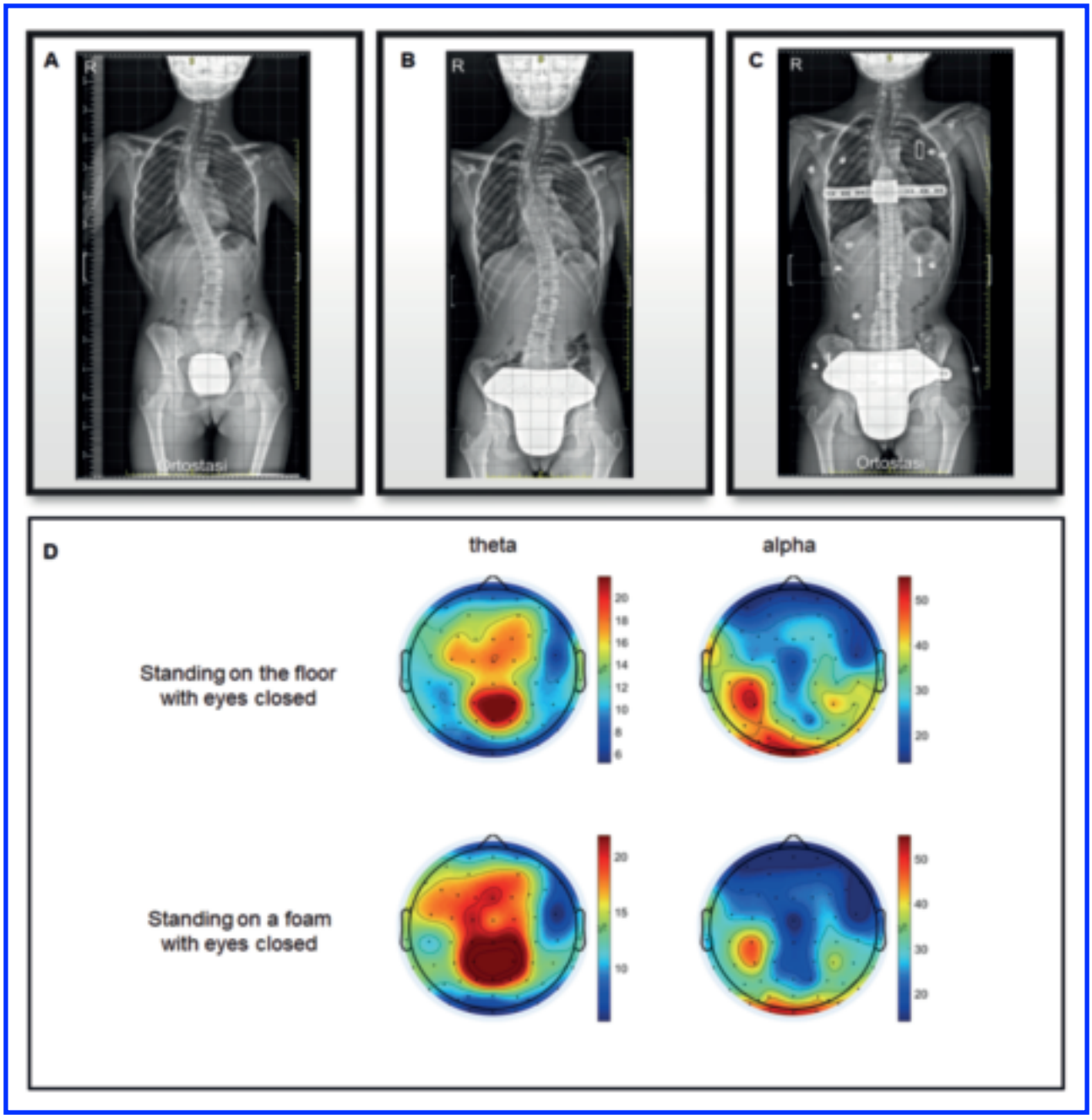

Figure 1. *A) This X-ray image shows the spine of the patient before the commencement of treatment for scoliosis; B) This X-ray image shows the spine of the patient after 8 months of conservative treatment; C) This X-ray, taken while wearing the brace 8 months after the initial X-ray assessment, shows the good correction performed by the orthosis; D) Relative EEG power (%) in theta [4.5-7.5] Hz and alpha [8-12] Hz bands while standing on the floor with eyes closed and standing on a foam with eyes closed.*

List of abbreviations

AIS, Adolescent Idiopathic Scoliosis
GH, growth hormone
EEG, electroencephalography

Contributions

SM and EF, development of the study design, supervision; MCM, MP, EP, PC, MR and EF, data collection, data interpretation; MCM, MR and EF writing; MCM, MR and EF data analysis.

Ethics approval

All methods were carried out in accordance with the guidelines of the 2008 Helsinki Declaration. Ethical approval has been obtained on April 2023 (5627/AO/22).

Informed consent

All patients participating in this study signed a written informed consent form for participating in this study.

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Conflict of interest

The authors declare no conflicts of interests.

Availability of data and materials

All data generated or analyzed during this study can be provided upon request.

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