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Case Report

Neurologic and Brain Magnetic Resonance Imaging (MRI) Abnormalities in a New XXYY Preadolescent Male

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Abstract

Background: Neuroimaging studies of XXYY preadolescent males are rare and the hemispheric white matter abnormalities that have been described thus far have not been consistently discussed.

Methods and Results: We present the case of an affected patient who exhibited mild intellectual and behavioral impairments, as well as a severe speech and language deficit. Brain neuroimaging revealed white matter hyperintensities distributed differently than in previous reports, with no features of lesion events.

Conclusion: We propose that these abnormalities result from altered oligodendrocyte myelination during development, particularly in the fronto-orbital regions, rather than from lesions.

Keywords: Neuroimaging; Oligodendrocyte Myelination; Brain Neuroimaging

Introduction

XXYY syndrome, also known as 48, XXYY syndrome, is a rare sex chromosome disorder and a variant of Klinefelter syndrome. Boys with this condition have an extra X chromosome and an extra Y supernumerary chromosome. Significant developmental impairments may include intellectual and learning disability, Attention Deficit Hyperactivity Disorder (ADHD), autism spectrum disorder, mood dysregulation and behavioral inappropriateness. Hypotonia, tremor and rare epileptic seizures may also occur [1-3]. Rare neuroimaging abnormalities, such as enlarged ventricles and focal hemispheric White Matter (WM) lesions, have been described and are generally attributed to tissue damage [2]. The WM hypersignals observed in this 48, XXYY child were in a slightly different location than those reported previously. The close relationship between sex hormones and glial cells, especially oligodendrocytes, during the early and late stages of brain development suggests that defective male neurosteroids play a role in causing myelin formation defects. This indicates that dysmyelination or focal hypomyelination is the underlying cause rather than lesional events.

Case Presentation

This adolescent male was born after a normal pregnancy and delivery. His morphometric parameters at birth were normal. He met his motor milestones on time, but a delay in language development was soon noted, initially impacting his phonological

and semantic abilities. Subsequently, slow syntactic and symbolic thinking, as well as poor verbal reasoning, became evident. At age nine, he was referred to a public neuropsychiatric service for evaluation for Autism Spectrum Disorder (ASD). He appeared excessively hesitant, avoided eye contact with the examiner and responded to basic questions with one-word answers, indicating possible cognitive impairment or a disorder on the ADHD spectrum. The patient presented with the following phenotypic anomalies: a turricephalic skull, a square forehead, a flat occiput, a flattened nasal root, a partially anteverted nasal tip, hypertelorism with bilateral epicanthal folds, shortened eyelids, an open bite and bilateral congenital elbow stiffness. Skeletal radiographs revealed bilateral radio-ulnar synostosis and dorsal scoliosis. The neurological examination was normal. The Occipitofrontal Circumference (OFC) was 52.5 cm, which is over 1.5 Standard Deviations (SD) above average. The initial Electroencephalographic (EEG) recording revealed rare, mostly frontal, irregular sharp waves. Genetic analysis by array-based Comparative Genomic Hybridization (aCGH) revealed 48, XXYY syndrome, which is caused by an extra X and Y chromosome. Magnetic Resonance Imaging (MRI) of the brain showed irregularly shaped, bilateral subcortical hypersignals that were slightly more prevalent in the right parietal-occipital WM and only occasionally periventricular. There was also minimal protrusion of the cerebellar tonsils into the occipital foramen, as well as a possible subtle developmental abnormality of the right hippocampus (Fig. 1,2).

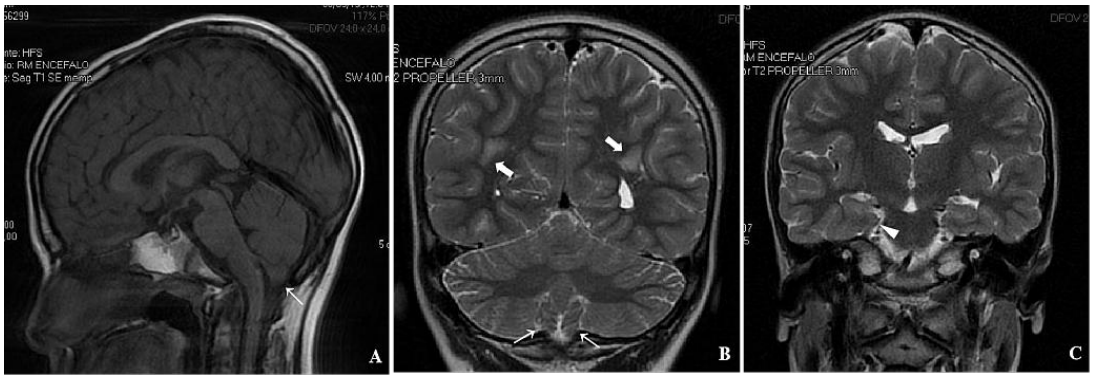

Figure 1: MRI images. Sagittal T1SE. (A) The CC is normal. Note the slight protrusion of the cerebellar tonsils into the foramen occipitale (thin arrow). Coronal T2 SE; (B) White matter abnormalities are present bilaterally (filled arrows). The slight protrusion of the cerebellar tonsils is confirmed. Coronal T2 SE; (C) In the right hippocampus, the subiculum and Ammon's horn are distinguishible with difficulty and the gray and white matter are blurred (filled arrowhead). The left hippocampus shows normal morphology. However, the entire temporal lobe appears underdeveloped with hyperfolding of its most inferior convolutions.

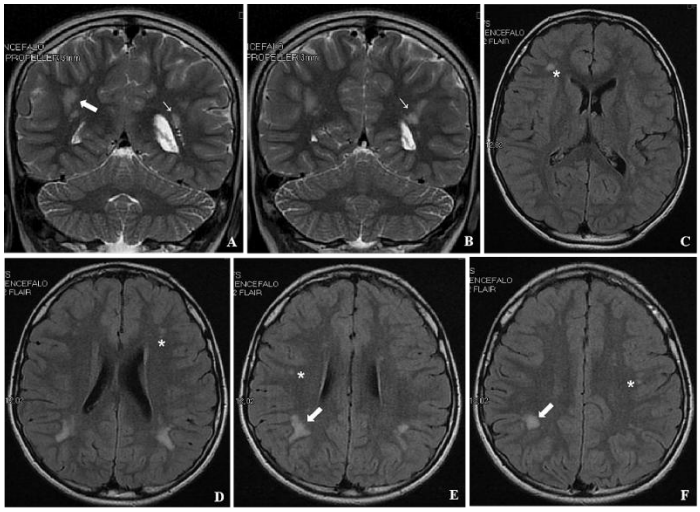

Figure 2: MRI images. Coronal T2 SE. (A and B) Bilateral WM hyperintensities appear large and subcortical on the right (filled arrow) and more peri/paraventricular on the left (thin arrow). The trigone of the left parietal lateral ventricle appears dilated. Axial T1 FLAIR; (C to F) The largest WM hypersignals are almost exclusively in the parietal lobes and are more prevalent on the right side (filled arrows). Many smaller abnormal signals can be seen more anteriorly, but always subcortically (small asterisks).

Discussion

This patient exhibited peculiarities that distinguished him from the few other rare cases reported in literature. A thorough neurological examination revealed no significant abnormalities and he did not exhibit tremors or other movement abnormalities, unlike the few patients described in previous studies [1-4]. As in most cases, his speech and language development were most affected. He was socially hesitant, though he did not experience alternating tantrums or friendship breakdowns. His intellectual abilities were borderline, yet he achieved satisfactory academic results with one-on-one support. His attention span was generally very short, though not identifiable as true ADHD. Epilepsy is rarely reported in individuals with XXYY syndrome [1-4]. This preadolescent male experienced occasional seizure-like events involving abnormal movements during sleep. However, repeated EEG recordings were normal. Rare structural brain abnormalities reported in XXYY aneuploidy include small frontal and periventricular WM lesions, thinning of the Corpus Callosum (CC) and enlarged ventricles [1,4,5]. However, these abnormalities were found in only six out of twenty-eight affected males [5]. An abnormal position of the cerebellar tonsils was rarely observed [5]. This case's brain MRI revealed normal lateral ventricles and slightly reduced hemispheric WM with bilateral focal hyperlucencies that were parietal rather than frontal and on the right side rather than the left. The hyperlucencies were subcortical and paraventricular rather than periventricular. The CC volume was normal. Additionally, the right hippocampal complex appeared dysmorphic due to subiculum and Ammon's horn tangles. The morphology of the right temporal horn of the laterl ventricle was abnormal as well. There was also slight protrusion of the cerebellar tonsils into the foramen magnum. The WM lucencies in this patient were less pronounced than those seen in true lesional injuries. Anxiety and depressive disorders are common in XXYY males during adolescence and preadolescence. This has prompted experimental studies and sophisticated human investigations, particularly brain imaging tractography. These studies have demonstrated sex-specific distributions of WM microarchitectural changes involving specific frontal and limbic systems, including association, commissural, projection and brainstem connections [6]. In particular, studies of fractional anisotropy and radial diffusivity have strongly suggested a causal role for alterations in myelination [7]. Because myelination is essential for effective neuronal communication, the loss of WM microstructural integrity may contribute to the pathophysiology of anxiety disorders and related conditions, including depression, behavioral and social inappropriateness and ADHD [7]. The WM abnormalities in our patient may have the same pathogenesis, which could explain his clinical condition. Furthermore, studies on Oligodendrocyte Progenitor Cell (OPC) development and oligodendrocyte biology have demonstrated that male OPCs are more sensitive to cytotoxic stress and more susceptible to apoptosis and cell death than female OPCs [8]. Sex hormones significantly impact the number, proliferation and functional maturation of glial cells, including oligodendroglial cells, primarily by activating Akt and mTOR. These pathways may therefore regulate oligodendrocyte differentiation [9]. In healthy individuals, Dihydrotestosterone (DHT) increases the expression of genes related to synaptic function and enhances neuronal electrical activity. This activity is a known inducer of myelination [10]. However, DHT is downregulated in XXYY patients. The various clinical and neuroimaging findings in this case reflect the range of clinical presentations observed in individuals with XXYY syndrome.

Conclusion

In conclusion, we propose that the intricate interplay between oligodendrocyte myelination and sex hormones during development may clarify WM abnormalities associated with XXYY aneuploidy and eliminate the possibility of a lesional origin.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Acknowledgement

The authors have no acknowledgments to declare.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

This study was conducted in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association.

Furthermore, the manuscript did not need the approval of the Ethical Committee of our University Administration as this is not a requirement for the publication of a single case provided that it is of definite interest to the scientific Community (Regulations of the Ethical Committee of "Area Vasta Emilia Nord", Italy, approved on September 22, 2020).

Informed Consent Statement

The informed consent has been obtained and the anonymity preserved.

Authors' Contributions

Conceptualization: E.D.G.; Data collection and analysis: O.C.; M.S.; Data curation: O.C.; P.B.; Investigation: P.B.; I.S.; Writing-original draft: E.D.G.; L.R.B.; Writing-review and editing: All authors.

References

1. Tartaglia N, Borodyanskaya BA, Hall DA. Tremor in 48,XXYY syndrome. Mov Disord. 2009;24(13):2001-7.
2. Taylor WD, Paine ME, Krishnan KR, et al. Evidence of white matter tract disruption in MRI hyperintensities. Biol Psychiatry. 2001;50(3):179-83.
3. Tartaglia NR, Ayari NA, Hutaff-Lee C, Boada R. Attention-deficit hyperactivity disorder symptoms in children and adolescents with sex chromosome aneuploidy: XXY, XXX, XYY and XXYY. J Dev Behav Pediatr. 2012;33(4):309-18.
4. Lote H, Fuller GN, Bain PG. 48,XXYY syndrome associated tremor. Pract Neurol. 2013;13(4):249-53.
5. Hanley AP, Blumenthal JD, Lee NR, Baker EH, Clasen LS, Giedd JN. Brain and behavior in 48,XXYY syndrome. Neuroimage Clin. 2015;8:133-9.
6. Aggarwal N, Tromp DPM, Blackford JU. Sex-specific distributed white matter microarchitectural alterations in preadolescent youths with anxiety disorders: A mega-analytic study. Am J Psychiatry. 2024;181:299-309.
7. Song SK, Yoshino J, Le TQ. Demyelination increases radial diffusivity in corpus callosum of mouse brain. Neuroimage. 2005;26(1):132-40.
8. Yasuda K, Maki T, Kinoshita H, et al. Sex-specific differences in transcriptomic and cellular characteristics of oligodendrocyte precursor cells. Stem Cell Res. 2020;46:101866.
9. Chong ZZ, Li F, Maiese K. The pro-survival pathways of mTOR and protein kinase B target glycogen synthase-3β and nuclear factor-κB to foster endogenous microglial cell proliferation. Int J Mol Med. 2007;19(2):263-72.
10. Zahaf A, Kassoussi A, Hutteau-Hamel T. Androgens show sex-dependent differences in myelination in immune and non-immune murine models of CNS demyelination. Nat Commun. 2023;14:1592.

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