

Double Cortex Syndrome in an Adolescent Female with Refractory Epilepsy and Consanguineous Parentage: A Case Report

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ABSTRACT

Double cortex syndrome, also known as Subcortical Band Heterotopia (SBH), is a rare X-linked dominant neuronal migration disorder caused by mutations in the Doublecortin (DCX) gene located at Xp22.3. It almost exclusively affects females, who present with variable degrees of epilepsy, developmental delay, and intellectual disability. We report an 18-year-old female born of second-degree consanguineous parentage who presented with multiple generalised tonic-clonic seizures and transient loss of consciousness. She had achieved normal developmental milestones until five years of age, when speech regression became apparent, followed by progressive learning difficulties and poor concentration during schooling. Physical examination confirmed global developmental delay. Electroencephalography (EEG) demonstrated epileptiform abnormalities. Computed Tomography (CT) of the brain revealed an abnormal band of grey matter deep to and paralleling the cortex bilaterally, raising the diagnosis of double cortex syndrome. Magnetic Resonance Imaging (MRI) of the brain confirmed bilateral symmetric subcortical grey matter bands isointense to normal cortex on all sequences, with frontoparietal cortical thickening and a thin intervening white matter layer creating the characteristic double cortex appearance. Antiepileptic therapy was initiated with referral for genetic counselling. This case underlines the critical role of MRI in the diagnosis of cortical malformations and the need for early genetic testing to guide management and family planning.

Keywords: DCX gene, Developmental delay, Epilepsy, Neuronal migration disorder

CASE REPORT

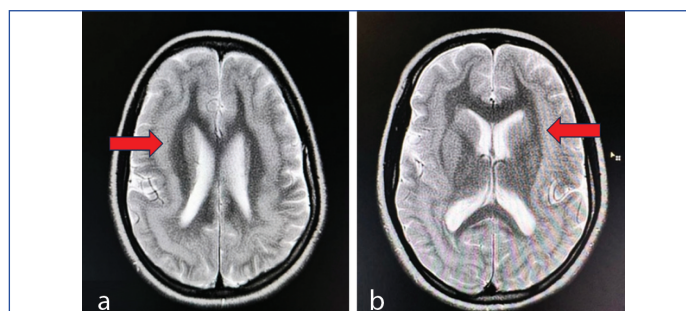
An 18-year-old female was brought to the hospital by her family with a history of recurrent generalised tonic-clonic seizures since the age of five years. She had experienced one to two seizure episodes every month, each lasting 2-3 minutes, characterised by generalised tonic-clonic movements with transient loss of consciousness, tongue bite, and spontaneous post-ictal recovery over 15-20 minutes. There was no history of aura, fever, neck stiffness, visual disturbances, head trauma, or meningitis. She had history of non adherence to her antiepileptic medication. No history of other precipitating factors such as sleep deprivation or fever. She had been receiving sodium valproate 500 mg twice daily since childhood, with only partial seizure control. She was the product of a full-term normal vaginal delivery with a normal Apgar score. Her parents were second-degree consanguineous relatives. She achieved normal developmental milestones until approximately five years of age, at which point a noticeable regression in speech was observed by her parents. Thereafter, she experienced progressive difficulty with learning and poor concentration, requiring additional academic support throughout her schooling years. She had no known comorbidities or history of substance use.

On examination, she was afebrile and haemodynamically stable. General physical examination was unremarkable; there were no dysmorphic features, neurocutaneous markers, or organomegaly. Neurological examination revealed global developmental delay. Motor tone, power, reflexes, and cerebellar function were within normal limits. Routine laboratory investigations - complete blood count, serum electrolytes including calcium, renal and liver function tests, and arterial blood gases - were all within normal limits. EEG demonstrated significant epileptiform abnormalities consistent with a generalised epileptic disorder.

The CT of the brain identified an abnormal band of grey matter located deep to and running parallel to the cortex bilaterally in both cerebral hemispheres, raising the suspicion of SBH. MRI of the brain was subsequently performed and confirmed the diagnosis. Axial and coronal T2-weighted sequences demonstrated bilateral symmetric subcortical

grey matter bands isointense to normal cortex, with thickening of the frontoparietal cortex. A thin layer of white matter separated the superficial cortical mantle from the heterotopic grey matter band, producing the pathognomonic 'double cortex' appearance [Table/Fig-1]. The overlying cortical mantle appeared mildly abnormal in the frontoparietal regions without overt agyria or pachygyria.

Alternative considerations in the differential diagnoses included focal cortical dysplasia, lissencephaly spectrum disorders, periventricular nodular heterotopia, tuberous sclerosis complex, and metabolic or structural causes of epilepsy. These were excluded based on the absence of characteristic clinical features and the MRI findings of bilateral symmetric subcortical grey matter bands separated from the cortex by a thin white matter layer, which are pathognomonic for double cortex syndrome - SBH [1]. She was treated with intravenous Levetiracetam 1 g/day during hospitalisation, followed by oral Levetiracetam 500 mg twice daily at discharge, while continuing Sodium valproate 500 mg twice daily. She remained seizure-free during hospitalisation and was discharged in a stable condition with advice on medication adherence, neurological follow-up, and genetic counselling. At the 3-month follow-up, seizure frequency was decreased to a single brief breakthrough episode, with good compliance to antiepileptic therapy and no new neurological deficits.



[Table/Fig-1]: MRI brain - axial T2-weighted sequences (A and B) demonstrating bilateral symmetric subcortical grey matter bands isointense to normal cortex (arrows), separated from the overlying frontoparietal cortex by a thin white matter layer, producing the characteristic double cortex appearance.

DISCUSSION

The SBH is a neuronal migration disorder arising from incomplete migration of neurons from the periventricular germinal matrix to the cortical plate during weeks 7-16 of embryogenesis [2]. Neurons that arrest at an intermediate position form a symmetric heterotopic grey matter band beneath the normal cortex - the anatomical substrate of the double cortex appearance on MRI. The disorder is caused in the vast majority of cases by mutations in the DCX gene at Xp22.3, which encodes DCX- a microtubule-associated protein essential for neuronal motility during cortical development [3]. The X-linked mosaicism that results from heterozygous DCX mutations in females explains why they typically manifest SBH rather than the more severe lissencephaly seen in hemizygous males [4].

Three categories of grey matter heterotopia are recognised: subependymal, subcortical, and band-like [5]. Band heterotopia is by far the most clinically significant. The severity of the associated epilepsy and the degree of cognitive impairment are directly proportional to the thickness of the heterotopic band and the extent of frontoparietal cortical involvement [6]. Epilepsy is intractable in approximately 65% of patients, requiring escalation through antiepileptic polytherapy, ketogenic diet, vagus nerve stimulation, or in carefully selected cases, epilepsy surgery [7].

The MRI is the diagnostic modality of choice and the imaging is characteristic: a bilateral, symmetric, continuous subcortical grey matter band isointense to cortex on all sequences, separated from the overlying cortex by intervening white matter [1]. A 2025 case report by Berrada K et al., confirmed that axial and coronal T2 sequences with thin-slice acquisition provide optimal delineation of the double cortex appearance and its extent [8]. Differential diagnoses include pachygyria - which lacks the intermediate white matter layer - and focal cortical dysplasia or tuberous sclerosis, which are typically asymmetric and localised.

The diagnosis was established on clinical and radiological grounds. The regression at five years, the progressive learning difficulties, and the frontoparietal cortical thickening on MRI are all well-documented features of juvenile-onset SBH in females [4]. A recent 2026 case study further confirmed that MRI can establish the diagnosis with high confidence even where genetic testing is unavailable, and that phenytoin or levetiracetam monotherapy achieves meaningful seizure control in a proportion of patients [9].

Developmental delay, epilepsy, and characteristic MRI findings were reported in previous case studies published by Afzal F et al., Berrada K, Nedday S et al., and Mahmud R [1,8,10,11]. Some patients can have refractory epilepsy like reported by Mahmud R [11]. Although recurrence of seizures in the case discussed in this case study was likely due to medication non-adherence.

CONCLUSION(S)

Double cortex syndrome should be considered in any female presenting with epilepsy and developmental delay, particularly when MRI reveals bilateral symmetric subcortical grey matter bands. This case highlights the pivotal role of MRI in diagnosing SBH. Early diagnosis, followed by genetic evaluation and counselling due to the association with DCX mutations, facilitates appropriate antiepileptic management and informed family planning. Expanding access to DCX gene testing in resource-limited regions remains a critical unmet need.

Declarations

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REFERENCES

- [1] Afzal F, Tabassum S, Naeem A, Naeem F, Ahmad RU. Double cortex syndrome (subcortical band heterotopia): A case report. *Radiol Case Rep.* 2023;18:671-74. <https://doi.org/10.1016/j.radcr.2022.11.021>.
- [2] Pang T, Atefy R, Sheen V. Malformations of cortical development. *The Neurologist* 2008;14:181-91. <https://doi.org/10.1097/NRL.0b013e31816606b9>.
- [3] Gleeson JG, Lin PT, Flanagan LA, Walsh CA. Doublecortin is a microtubule-associated protein and is expressed widely by migrating neurons. *Neuron.* 1999;23:257-71. [https://doi.org/10.1016/s0896-6273\(00\)80778-3](https://doi.org/10.1016/s0896-6273(00)80778-3).
- [4] Dobyns WB, Andermann E, Andermann F, Czapansky-Beilman D, Dubeau F, Dulac O, et al. X-linked malformations of neuronal migration. *Neurology.* 1996;47:331-39. <https://doi.org/10.1212/wnl.47.2.331>.
- [5] Abdel Razek AAK, Kandell AY, Elsorogy LG, Elmongy A, Bassett AA. Disorders of cortical formation: MR imaging features. *AJNR Am J Neuroradiol.* 2009;30:4-11. <https://doi.org/10.3174/ajnr.A1223>.
- [6] Watrin F, Manent J, Cardoso C, Represa A. Causes and consequences of Gray matter heterotopia. *CNS Neurosci Ther.* 2014;21:112-22. <https://doi.org/10.1111/cns.12322>.
- [7] Parisi P, Miano S, Mei D, Paolino MC, Castaldo R, Villa MP. Diffuse subcortical band heterotopia, periodic limb movements during sleep and a novel "de novo" mutation in the DCX gene. *Brain Dev.* 2010;32:511-15. <https://doi.org/10.1016/j.braindev.2009.06.007>.
- [8] Berrada K. Double cortex syndrome A striking case of X linked subcortical band heterotopia. *J Clin Images Med Case Rep.* 2025;6. <https://doi.org/10.52768/2766-7820/3698>.
- [9] Shukralla NA, Hunde WM, Tibebe M, Dida MK. Subcortical band heterotopia in a child with new-onset seizures: A case report. *Epilepsy Behav Rep.* 2026;33:100852. <https://doi.org/10.1016/j.ebr.2026.100852>.
- [10] Nedday S, Naji Y, Assardoun M, Laadami S, Adali N. Double cortex syndrome: An unusual cause of seizures. *Cureus.* 2024;16:e63507. <https://doi.org/10.7759/cureus.63507>.
- [11] Mahmud R. Subcortical band heterotopia presented with refractory epilepsy and reversible aphasia. *Cureus.* 2021;13:e16990. <https://doi.org/10.7759/cureus.16990>.

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