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Sleep spindle activity in double cortex syndrome: a case report

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ABSTRACT – Cortical dysgenesis is increasingly recognised as a cause of epilepsy. We report a case with double cortex heterotopia and secondarily generalized seizures with a generalised spike wave pattern. During the course of the disease, the child developed electrical status epilepticus in slow wave sleep. From the first examination, sleep pattern revealed increased frequency and amplitude of spindle activity, more evident in anterior areas. The role of the thalamocortical pathway in increased sleep spindle activity is discussed with emphasis on the possible role of altered thalamocortical pathways in abnormal cortical migration. A strong suspicion of cortical dysgenesis may therefore be based on specific EEG sleep patterns.

Key words: sleep, spindles, epilepsy, EEG, cortical dysgenesis, double cortex syndrome

Double cortex (DC) syndrome, *i.e.* subcortical laminar heterotopia, is a rare genetic disorder of neuronal migration which is seen almost exclusively in females and associated with mental retardation and epilepsy. In DC and X-linked lissencephaly (LYS), neurons leaving the ventricular zone during development fail to reach the cortex, leading to mental retardation and epilepsy (Harding, 1996). In DC, the migration of a subset of cortical neurons arrest before completion to form a "double" cortex, which is a band of grey matter located within the subcortical white matter. LYS results from the failure of proper migration of cortical neurons, leading to a much more severe disorder of cortex development. For both malformations, a mutation of the gene doublecortin on chromosome Xq22.3-q24 in females with DC and in males with LYS (Gleeson *et al.*, 1998) has been demonstrated.

Previous clinical (Mori *et al.*, 1994) and experimental (Majkowski *et al.*, 1984) studies of LYS have reported electroencephalographic (EEG) abnormalities consisting of slowing of background activity, extreme spindle activity, focal or multifocal sharp waves, spikes and spike-and-slow wave complexes. Given the rarity of DC syndrome, there are no reported case studies of DC patients with sleep EEG monitoring. However, patients with DC may present the same sleep alterations as patients with LYS, namely focal or multifocal epileptic discharges and increased spindling. In the present report we describe serial sleep EEG studies in a patient diagnosed with DC.

Case study

The 14-year-old female patient's perinatal history was unremarkable although her early psychomotor development was slightly slow. Her father had febrile convulsions. When she was eight months old her epilepsy began with partial seizures and

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secondarily generalised tonic-clonic seizures and she responded to carbamazepine therapy. She was admitted to our institution at age 11 because seizures had changed to become jerks during sleep and on awakening, with nocturnal wandering. Her cognitive abilities declined.

EEGs during wakefulness showed bilateral, synchronous generalised spikes and slow sharp waves, more pronounced in the frontal and anterior temporal areas and in the right hemisphere. The first sleep EEG study showed electrical status epilepticus in non-rapid eye movement (NREM) sleep and bifrontal and frontotemporal spikes in rapid eye movement (REM) sleep. Sleep structure showed the presence of longer spindles at a frequency of 13 Hz, associated with the EEG paroxysms. Brain MRI revealed ventricular dilatation and bilateral subcortical heteropic bands in anterior areas.

Under carbamazepine, levetiracetam and clobazam tritherapy for one year, the frequency of seizures improved with complete absence of seizures during the awake state. No nocturnal wanderings or spasms were reported during sleep. Repeated sleep monitoring showed the persistence of polyspike waves and sharp waves during wakefulness *(figure 1A)* without critical events. During sleep, recognition of sleep stages was possible and sleep scoring allowed classification of light, slow and REM sleep. Analysis of phasic EEG events during NREM sleep *(figure 1B)* revealed a higher density of sleep spindles with a frequency of 13-14 Hz, bilaterally present in all cerebral areas but longer and with greater density in anterior sites. REM sleep *(figure 1C)* induced a significant reduction of generalised spike frequency. Comparison of spectral EEG analysis during NREM sleep between a control subject matched for age and the patient at the first examination *(figure 2A, B)* confirmed the visual analysis *(figure 2, left side)*, *i.e.* an increase in sigma frequency in the 13.5 range and an increase in relative power in the same EEG frequency band. A second nocturnal recording was performed after clobazam withdrawal. As shown in *figure 2C*, spectral EEG analysis showed the persistence of increased power activity in the range of 13.5 Hz, more evident in the anterior areas.

Discussion

To the best of our knowledge, this report is the first to objectively document sleep EEG pattern in a patient with double cortex syndrome. The most interesting finding is the presence of high amplitude prolonged and diffuse spindles with a prevalence in the anterior areas during NREM sleep. This EEG feature is similar to sleep-spindle alterations reported in LYS, underlying the similarity in phenotype between DC syndrome and LYS. Thus, EEG spindle activity could be used as a neurophysiological marker of abnormal maturational processes.

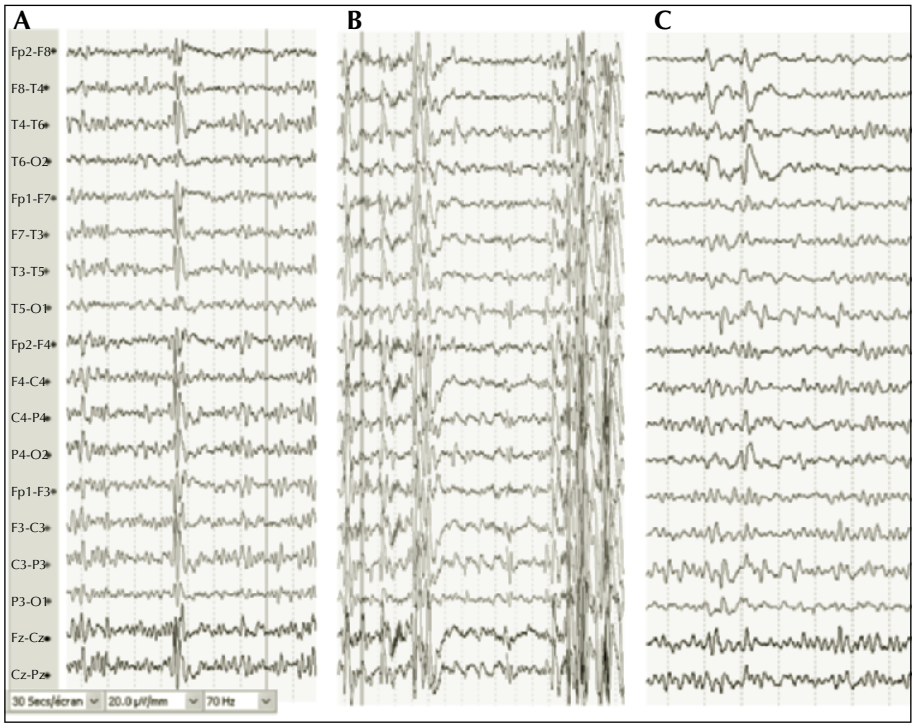

Figure 1. Representative sleep EEG recording during **A**) wakefulness, **B**) NREM sleep and **C**) REM sleep. In NREM sleep, generalised spike discharges and slow wave discharges were recorded, while a reduction of epileptic discharges in REM sleep occurred. During NREM sleep prolonged bilateral spindle activity was found mixed with epileptic discharges (**B**).

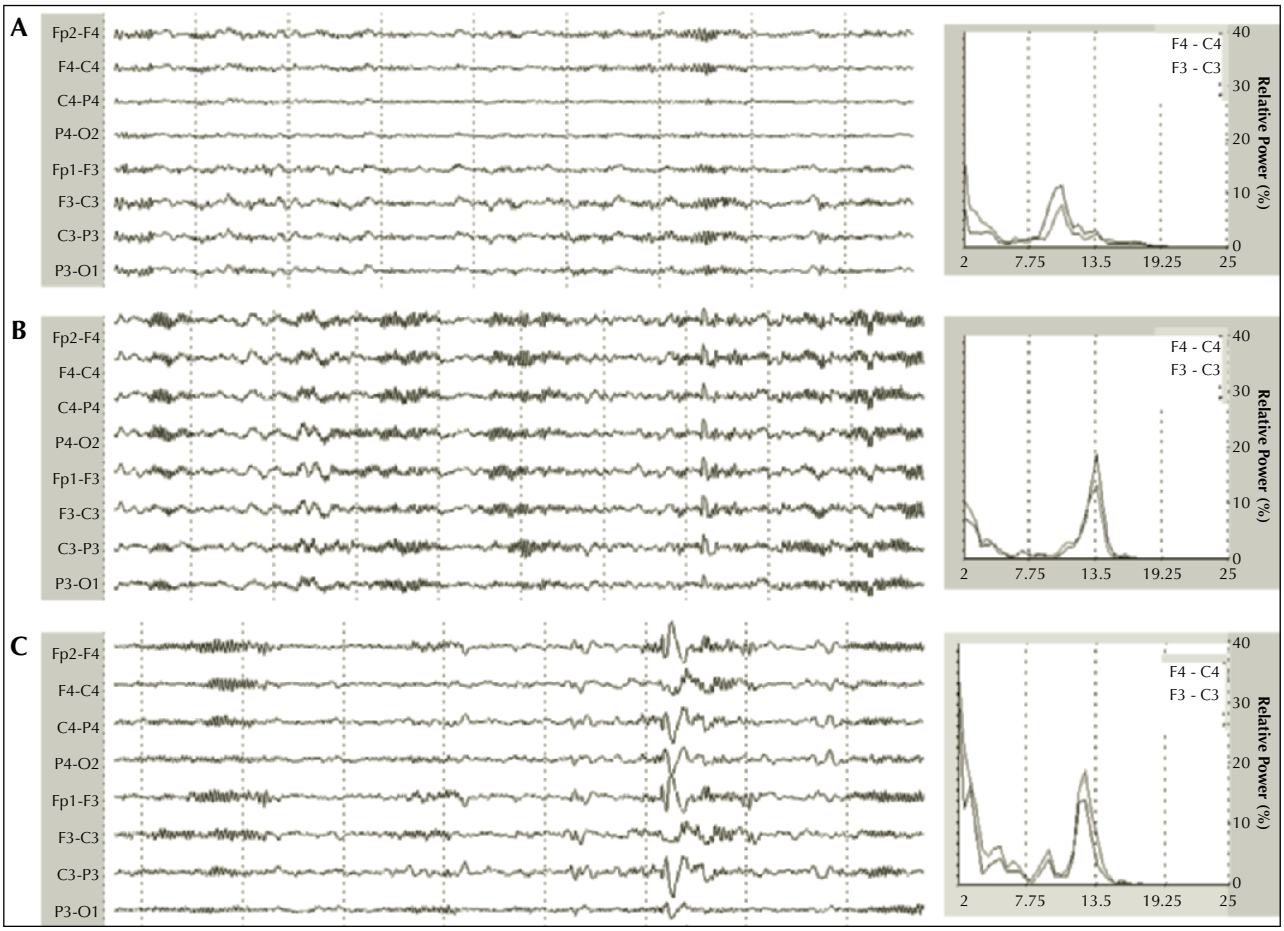

Figure 2. Examples of sleep EEGs and spectral EEG analysis during stage 2 of NREM sleep. **A**) Age-control subject. **B**) Patient when treated with carbamazepine, levetiracetam and clobazam. **C**) One month after interruption of clobazam. Compared to the control, the patient had prolonged spindles lasting three seconds with an amplitude greater in anterior areas and persisting after clobazam interruption (**C**). Spectral analysis performed in the same 20-second EEG period (on the right) shows a rise in delta activity, compared to the control, related to the presence of epileptic K-complexes and an increase in power for the 13-14 Hz band frequency indicating increase in frequency and amplitude of spindles. This pattern persisted after clobazam interruption with the relative power still greater in the patient and in the anterior areas.

The atypical spindle activity present in patients with DC syndrome may be interpreted as a consequence of morphological brain changes and alterations of corticothalamic pathways related to the extent of malformation. The few studies analysing sleep microstructure in disorders of migration showed the presence of diffuse sleep spindles (Mori *et al.*, 1994) as well as high amplitude spindling and fast dysrhythmia in alpha and beta frequency bands (Gastaut *et al.*, 1987; Selvitelli *et al.*, 2009). In these migration malformations, migrating neural cells arrest in the subcortical white matter between their starting point and normal targets (Harding, 1996), and MRI shows cortical thickening and simplified gyration. The thickness of heterotopic cortex and degree of pachygyria differentiate lyssencephaly in males and double cortex in females, as well as the severity of mental retardation and epilepsy. Sleep spindles are distinctive phasic events arising from NREM sleep and prevalent in stage 2 of NREM sleep. Neurophysiologically, it has been shown that spindle generation involves thalamic neurons and corticothalamic networks (Steriade, 2005). The neural generators of phasic sleep EEG activities, *i.e.* spindles and K-complexes, promote seizure propagation during NREM sleep (Shouse *et al.*, 2000) and facilitate epileptiform discharges on the cortex (Nobili *et al.*, 2001). Therefore, it could be postulated that, as for other brain malformations (Selvitelli *et al.*, 2009), an alteration of information transfer from the thalamus to neocortical sites in DC syndrome may be related to altered thickness of the cortex and increased flow of thalamocortical projection. If so, an increased spindle activity during NREM sleep will occur, with spindles lasting longer and of greater amplitude. In line with this hypothesis, an experimental study (Majkowski *et al.*, 1984) demonstrated that neocortical volume and size affect the frequency and amplitude of generated thalamic spindling, thickness of the cortex gen-

erated on the scalp and are associated with a spindle activity of greater frequency and amplitude. Alternatively, an anatomical and functional interconnection between the normal and heterotopic cortices (Mai *et al.*, 2003) may be proposed as a mechanism of increased spindling in patients with cortical heteropia.

One limitation of our study is that the comparison between the age-control subject and our patient was performed when our patient was receiving treatment. However, the FFT analysis performed after clobazam interruption suggests that the increase in duration and frequency of spindles cannot be explained by the benzodiazepine treatment alone.

In conclusion, our observation suggests that increased spindle activity and the presence of rapid and high amplitude spindles may be a neurophysiological predictor of abnormal neural migration disorders such as LYS and DC syndrome. The atypical spindle activity during sleep could reveal the influence of the altered thickness of the cortex on thalamocortical pathways. Further studies of large samples of patients are needed to confirm the usefulness of this neurophysiological parameter in the diagnosis of neural migration malformations. □

Disclosure
None of the authors has any conflict of interest or financial support to disclose.

References

Gastaut H, Pinsard N, Raybaud C, Aicardi J, Zifkin B. Lissencephaly (agyria-pachygyria): clinical findings and serial EEG studies. *Dev Med Child Neurol* 1987; 29: 167-80.

Gleeson JG, Allen KM, Fox JW, *et al.* Doublecortin, a brainspecific gene mutated in human X-linked lissencephaly and double cortex syndrome, encodes a putative signaling protein. *Cell* 1998; 92: 51-61.

Harding B. Gray matter heterotopia. In: Guerrini R, *et al.*, eds. *Dysplasias of cerebral cortex and epilepsy*. Philadelphia: Lippincott-Raven, 1996: 81-8.

Majkowski J, Lee MH, Kozlowski PB, Haddad R. EEG and seizure threshold in normal and lissencephalic ferrets. *Brain Res* 1984; 307: 29-38.

Mai R, Tassi L, Cossu M, Francione S, *et al.* A neuropathological, stereo-EEG and MRI study of subcortical band heterotopia. *Neurology* 2003; 60: 1834-8.

Mori K, Hashimoto T, Tayama M, *et al.* Serial EEG and sleep polygraphic studies on lissencephaly (agyria-pachygiria). *Brain Dev* 1994; 16: 365-73.

Nobili L, Baglietto MG, Beelke M, *et al.* Distribution of epileptiform discharges during NREM sleep in the CSWSS syndrome: relationship with sigma and delta activities. *Epilepsy Res* 2001; 44: 119-28.

Selvitelli MF, Krishnamurthy KB, Herzog AG, Schomer DL, Chang BS. Sleep spindle alterations in patients with malformations of cortical development. *Brain Dev* 2009; 31: 163-8.

Shouse MN, Farber PR, Staba RJ. Physiological basis: how NREM sleep components can promote and REM sleep components can suppress seizure discharge propagation. *Clin Neurophysiol* 2000 (Suppl. 2): S9-18.

Steriade M. Sleep, epilepsy and thalamic reticular inhibitory neurons. *Trends Neurosci* 2005; 28: 317-24.