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. sub-cortical 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
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 tri-therapy 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).](image-url)
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 ampli-
titude spindling and fast dysrhythmia in alpha and beta fre-
quency bands (Gastaut et al., 1987; Selvitelli et al., 2009).

In these migration malformations, migrating neural cells arrest in the subcortical white matter between their start-
ing point and normal targets (Harding, 1996), and MRI shows cortical thickening and simplified gyration. The thickness of heterotopic cortex and degree of pachygryia differentiate lissencephaly 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 dis-
charges 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-

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.
Sleep spindles in double cortex


