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Clinical Medicine Insights: Case Reports

Narcolepsy Associated with Duane's Syndrome

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ABSTRACT: The best characterised disorder of REM sleep, narcolepsy has never previously been associated with Duane's syndrome, in which there is developmental failure of the abducens nerve and its nucleus. The major brain stem nuclei responsible for REM sleep generation are situated in the pons in close proximity to the abducens nerve nucleus. We report the novel combination of Duane's syndrome and narcolepsy, providing new insight into the pathogenesis of narcolepsy.

KEY WORDS: narcolepsy, Duane's syndrome, cataplexy, congenital disorder, pons

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Introduction

Duane's syndrome is a rare congenital disorder of the sixth (abducens) nerve and sixth nerve nucleus in the pons, with aberrant innervation of the lateral rectus muscle by the third (oculomotor) nerve.[1] The major brain stem nuclei that generate rapid eye movement (REM) sleep, the pedunculopontine and laterodorsal tegmental nuclei (PPN/LDT), together with the sublaterodorsal tegmental nuclei (SLD), are located within the pons,[2] in close proximity to the sixth nerve nucleus. The best characterised disorder of REM sleep, narcolepsy, has not previously been associated with Duane's syndrome. Here we report the first patient with this combination of conditions.

Case History

A male patient in his late teens with previously diagnosed Duane's syndrome affecting his left eye was referred to the Sleep Centre at Papworth Hospital, Cambridge with excessive daytime sleepiness that had worsened over the previous one to two years, despite 9–10 hours of sleep each night. He had fallen asleep during examinations and even while at sea on a surfboard. He had sleep paralysis at sleep onset. When he laughed, he had difficulty in speaking, experienced head nodding, dropped objects and his jaw had fallen open. He had no hypnagogic hallucinations, but did have vivid realistic dreams in color and sound involving flying or diving under water. There was no relevant family history or any other previous sleep disorder. His Epworth Sleepiness score was 17 (maximum 24, normal less than 11).

At polysomnography his sleep latency was 8 minutes, but REM sleep latency was 187.5 minutes. His REM sleep occupied only 14.2% of his total sleep time. No other abnormalities were present. His mean multiple sleep latency testing (MSLT) was 18.3 minutes and there were no REM sleep episodes. HLA testing was negative for HLA DQB1 ^{x}0602. CSF hypocretin is not currently available for general clinical use in Papworth hospital and therefore was not tested. MRI brain showed no structural abnormality in the pons.

He was treated with Modafinil up to 600 mg daily, which improved his most troublesome symptom, his daytime sleepiness. His cataplexy persisted over two years of observation.

Discussion

Duane's syndrome leads to absent or limited abduction of the affected eye, restricted adduction and associated abnormal

vertical eye movements, retraction of the globe and narrowing of the palpebral fissure.[3] Inheritance usually follows an autosomal dominant pattern with loci for abnormal genes being identified at 4q, 8q, and 22q.[1] Duane's syndrome has been associated with ocular anomalies including heterochromia, iris dysplasia, colobomas and Marcus-Gunn phenomena, as well as systemic anomalies including Goldenhar's syndrome, Klippel-Feil syndrome and sensorineural deafness.[4]

Narcolepsy is due to instability of the control of REM sleep and wakefulness, so that fragments of REM sleep such as sleepiness, hallucinations and muscle weakness (sleep paralysis and cataplexy) intrude into wakefulness. This patient had each of these features except for hypnagogic hallucinations, but also had vivid realistic dreams, which are a feature of narcolepsy. Importantly, he had definite episodes of cataplexy, which is specific for the diagnosis of narcolepsy. He did not have sleep onset REM sleep on either his polysomnography or MSLTs, but this may have been because of difficulty in scoring REM sleep as a result of his Duane's syndrome restricting lateral movement of his left eye. Nevertheless, his combination of excessive sleepiness and cataplexy fulfils the international criteria for the diagnosis of narcolepsy as stipulated by the International Criteria for Sleep Disorders.[5]

Idiopathic narcolepsy is almost invariably associated with HLA DQB1*0602. This HLA type was absent in this patient, suggesting that his narcolepsy had a different pathogenesis. Evidence for absence of the sixth nerve nucleus in Duane's syndrome stems from clinical-pathological studies[6] and has not yet been demonstrated using MRI in published literature; thus the lack of abnormality detected in the pons on MRI neither refutes nor augments our hypothesis. Organic brain disorders, particularly those affecting the hypothalamus and nearby brain stem, can cause narcolepsy but the clinical features are usually atypical, with prominence of visual hallucinations during the day or the absence of typical cataplexy.[7] Case reports have suggested associations between narcolepsy with cataplexy and both agenesis of the corpus callosum with elevation of the third ventricle and holoprosencephaly.[8,9] Cataplexy alone has been reported to be associated with the rare congenital neurological condition Moebius syndrome, in which hypoplasia of cranial nerves VI and VII results in facial paralysis and impaired lateral eye movement.[10] Our patient, however, had typical clinical features of idiopathic narcolepsy, suggesting that the abnormality related to his Duane's syndrome damaged precisely, and apparently selectively, the REM sleep-generating systems in the pons that are dysfunctional in narcolepsy, but through a different mechanism than in idiopathic narcolepsy.

We propose narcolepsy should be considered in those presenting with the phenotype Duane's syndrome and, conversely, abnormalities of control of the extra-ocular muscles should be sought in patients presenting with features of otherwise classical idiopathic narcolepsy.

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Author Contributions

Conceived and designed the experiments: JMS. Analyzed the data: JWB, JMS. Wrote the first draft of the manuscript: JWB. Contributed to the writing of the manuscript: JMS. Agree with manuscript results and conclusions: JWB, JMS. Jointly developed the structure and arguments for the paper: JWB, JMS. Made critical revisions and approved final version: JWB, JMS. All authors reviewed and approved of the final manuscript: JWB, JMS.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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