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Anti-Ma2-associated paraneoplastic encephalitis eat, sleep and repeat

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Eat, Sleep and Repeat

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Anti-Ma2 associated paraneoplastic encephalitis

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Abstract:

Anti-Ma2 associated paraneoplastic encephalitis (PNE) is a syndrome characterised by dysfunction of the diencephalon, brainstem and limbic systems. We describe a rare presentation with narcolepsy type 1 and a REM sleep behaviour disorder to promote familiarity amongst general and respiratory physicians who will potentially be the first to encounter these patients. An early diagnosis potentially ensures a favourable prognosis.

More familiar presentations of paraneoplastic encephalitis (PNE) include seizures, depression and cognitive decline. A rare cause described is antibodies against the onconeural protein Ma2¹. Increasing experience suggests that it differs from other forms of PNE². We describe a case that highlights this contrasting presentation.

A 35-year-old male suffered from excessive day time sleepiness (EDS) which worsened over 6-months, requiring up to 16-hours of sleep daily. Sleep periods were characterised by dream-enacting behaviour. He further experienced sugar cravings, waking only to seek carbohydrates. Brainstem dysfunction developed with diplopia progressing to vertical ophthalmoparesis. Frontal cognitive impairment, the only classical PNE feature to emerge, became apparent 2-years after the initial presentation.

Sleep review resulted in a diagnosis of narcolepsy type 1 (NT1) with a rapid eye movement (REM) sleep behaviour disorder (RBD). Polysomnography and Multiple Sleep Latency Testing showed a mean sleep latency of 2.8 minutes and multiple periods of REM sleep occurring 15 minutes from sleep onset. HLA genotyping was not performed. The narcolepsy was unresponsive to both non-amphetamine and amphetamine agents.

Other investigations were only pursued when further progression occurred. MRI brain showed FLAIR hyperintensities in the right medial temporal lobe and CSF analysis demonstrated a protein of 0.54g/L and 4 lymphocytes. The EEG suggested encephalopathy. Basic bloods and initial cerebral Tc-99m-hexamethylpropylene amine oxime imaging were unremarkable. Anti-Ma2 antibodies were isolated in the CSF and serum at a titre of 1:10 and 1:160 respectively while other paraneoplastic antibodies were undetected. Malignancy screening with CT, FDG-PET scan and testicular ultrasound were negative. Bilateral orchidectomy was pursued given a known association¹ and histopathology demonstrated diffuse intratubular germ cell neoplasia.

Steroids, immunoglobulins, cyclophosphamide and rituximab were used in combination following tumour resection. Mild neurological improvement was initially observed but stagnated. No single immunotherapy appeared more effective. Repeat cerebral SPECT imaging showed increasing right temporal perfusion correlating with increasing flair hyperintensity in the right temporal region. The development of refractory temporal pole seizures contributed to further neurological disability and ultimately death.

To our knowledge this is the third documented case of anti-Ma2 associated encephalitis presenting with NT1 and a RBD²⁻⁴. However EDS has been noted in up to 32% of cases². Idiopathic NT1 is caused by selective loss of the hypothalamic hypocretin-synthesizing neurons³. Hypocretin promotes wakefulness and inhibits REM sleep. Low or undetectable levels in these subjects suggest a similar pathogenesis²⁻⁴. 98% of subjects with idiopathic NT1 carry the HLA-DQB1*0602 allele⁵. Tested in one of the three cases, the absence of the allele emphasises the importance of HLA genotyping³.

While death was the outcome in this case, analysis of 38 cases have demonstrated neurological improvement or stabilization in 50% of patients following treatment². Limited CNS involvement at diagnosis and a tumour responsive to therapy were favourable prognostic features². This case illustrates the initial presentation of anti-Ma2 associated encephalitis with NT1 and RBD. It highlights the importance of a heightened clinical suspicion amongst sleep physicians to ensure an early diagnosis. In retrospect, HLA genotyping as a part of the sleep review, may have prompted a timelier diagnosis.

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