A case of a patient with multiple sclerosis and Kallmann syndrome

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Introduction: Kallmann syndrome (KS) is a genetic disorder characterized by hypogonadotrophic hypogonadism and anosmia, occurring both in sporadic and inherited forms, including autosomal dominant, autosomal recessive and X-linked recessive transmission patterns.
Recently, a case of a 34-year-old man with KS who developed multiple sclerosis (MS) has been reported.

Case report: A 26-year-old woman came to our attention complaining of progressive paraesthesia and hypoesthesia over the lower limbs from 4 days. She had been diagnosed with KS a few years before on the basis of anosmia, confirmed by smell test, and hypogonadotrophic hypogonadism, with no response to LHRH test. Karyotype was 46-XX. Elevated levels of 17-OHP were found. She was treated with estroprogestin therapy. Screening tests for KS genetic mutation, performed in another centre, turned out negative whilst she resulted positive for homozygous mutation of C677T methylenetetrahydrofolate reductase (MTHFR) and therefore she was treated with acid folic supplementation. At the age of 11, she presented with transient binocular visual impairment interpreted as bilateral optic neuritis. Brain magnetic resonance imaging (MRI) showed two periventricular lesions without gadolinium enhancement. Over the following years these findings remained unchanged at the neuroradiological follow up.
Despite the disease, she had no cognitive impairment and she had graduated.
On admission, neurological examination revealed multi modal hypoesthesia at lower limbs with sensory level below the iliac crest, brisk deep tendon reflexes at four limbs, normal strenght, coordination and sphincter function. Plantar responses were flexor, there was no Hoffman sign. Her cognitive status was normal.
Brain MRI showed one new infratentorial T2-weighted hyperintense lesion without enhancement as well as the two lesions already detected on previous MRIs. Olfactory bulb volume was reduced, olfactory sulci and tracts resulted normal. Spinal cord MRI showed two T2-weighted hyperintense lesions over the dorsal tract at the level of D4-D5 and D7-D8, both with gadolinium enhancement. Cerebrospinal fluid examination disclosed the presence of oligoclonal bands at isoelectrofocusing. On the basis of these findings, the patient was treated with high doses of methylprednisolone i.v. (1 g a day for 5 days) with significant improvement. According to the 2010 Mc Donald's criteria [3], diagnosis of MS was established and therapy with subcutaneous glatiramer acetate 20 mg daily was started. The patient presented no relapse in a six months clinical follow up.

Discussion and conclusions: Brain MRI abnormalities have been previously described in patients with KS: a study on 45 male KS patients showed significant morphologic and structural alterations, especially on the gyri recti and the contiguous medial orbital-frontal regions. In this study only one patient showed white matter MS-like abnormalities.
Several genes have been connected with KS, which account for just 30% of patients with KS being the genetic defects unknown in all the other cases. Some of these genes are proven to be involved in the Anosmin1-FGF-FGFR signalling pathway, which regulates demyelination and remyelination processes, olfactory tract and hypothalamus development. Furthermore, the same proteins have been found in the MS plaques raising the hypothesis that those might also be involved in demyelination of MS.
Although the genetic abnormalities are not known in our case, on the basis of the data available about the Anosmin1-FGF-FGFR complex, we hypothesize the dysfunction of a protein involved both in inflammatory demyelination and in the other features of KS of our patient. In fact, anosmin-1 has a diffusible nature and it would exert opposing effects depending on the binding dynamics to FGF2–FGFR1–HS complexes.
We hypothesize that the abnormal protein not only leads to olfactory and hormonal dysfunction, but also may render myelin sheets more prone to the autoimmune damage of MS and/or less capable of repairing after the autoimmune injury. Of course, our observation is purely clinical and certainly more cases like our are needed to corroborate the possible association between KS and MS. The precise involvement of KS syndrome genes, if any, in autoimmune demyelination in KS patients with MS requires experimental pathological data. Furthermore, more genetic studies on the 70% of KS without a known genetic mutation are mandatory for a better understanding of all mechanisms underpinning this intriguing medical condition and its neurological complication including demyelinating diseases.

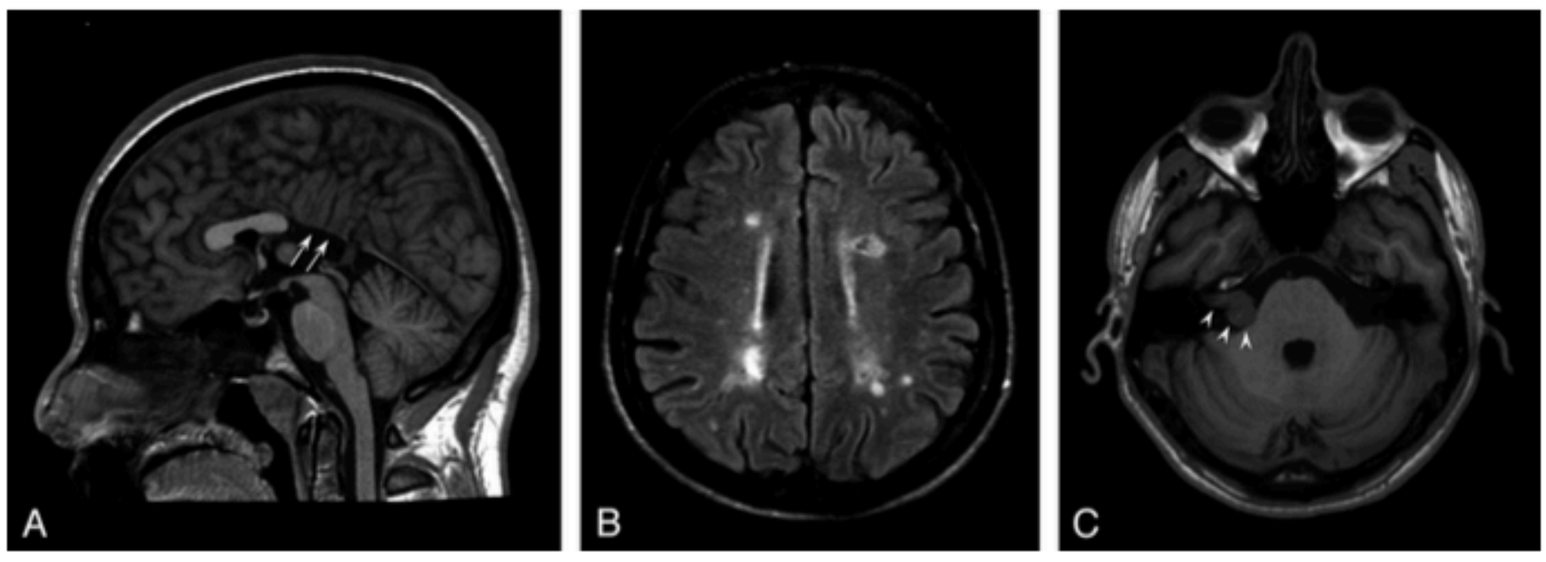

FIG 1. Conventional brain MR imaging findings in 45 patients with Kallmann syndrome. *A*, Midsagittal T1-weighted image of a patient with agenesia of the posterior portion of the corpus callosum (*white arrows*). *B*, Axial FLAIR image of the patient disclosing several multiple sclerosis–like white matter signal abnormalities in the centrum semiovale bilaterally. *C*, Non-enhanced axial T1-weighted image at the level of the internal acoustic meatus showing a right intra/extrameatal dumbell-shaped mass consistent with an acoustic schwannoma.

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