Is There an Increased Risk of Multiple Sclerosis in Individuals With Congenital Adrenal Hyperplasia?

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Background: Congenital adrenal hyperplasia (CAH) is an inherited recessive disorder of adrenal steroidogenesis, generally caused by a total or partial deficiency in 21-hydroxylase, due to a deletion or mutations in the CYP21 gene (which codes for 21-hydroxylase). Impaired cortisol biosynthesis results in corticotropin hypersecretion, which leads to overproduction of intermediate metabolites and androgens.

Objective: To describe for the first time, to our knowledge, a patient with CAH and multiple sclerosis (MS).

Design: Case report.

Patient: A 22-year-old woman, diagnosed at birth as having a salt-losing 21-hydroxylase deficiency, had sudden visual loss in the right eye and pyramidal, sensory, and cerebellar signs. Evidence of a congenital salt-wasting 21-hydroxylase deficiency consisted of ambiguous external genitalia, hyponatremia, hyperkalemia, and high levels of 17α-hydroxyprogesterone, corticotropin, and renin. Appropriate hydrocortisone and fludrocortisone treatment produced a good outcome. The CAH diagnosis was subsequently confirmed by the detection of a homozygote N172I mutation of the CYP21 gene on chromosome 6.

Results: The reported case fulfills the diagnostic criteria for CAH and MS.

Conclusions: Some clues suggest that the association between CAH and MS could be nonincidental: a possible MS susceptibility locus is on chromosome 6p21, on which the CYP21 gene is located, the CYP21 gene and the CYP21P pseudogene alternate in tandem with the C4 genes (the genes that code for the homonym complement protein); and, in previous studies, brain magnetic resonance imaging showed T2-hyperintense focal areas in the white matter of CAH patients.


C A N O N I T A L A D R E N A L H Y P E R P L A S I A (CAH) is a group of inherited recessive disorders of adrenal steroidogenesis, due to deficiency in one of the enzymes in the synthetic pathway. The most common form of CAH is caused by a 21-hydroxylase deficiency. The 21-hydroxylase deficiency is due to a deletion or mutations in the CYP21 gene (which codes for 21-hydroxylase), which is located in the HLA histocompatibility complex on chromosome 6. Adrenal enzyme deficiency causes an underproduction of cortisol and, in turn, hypersecretion of corticotropin. High plasma corticotropin levels lead to overproduction of intermediate metabolites, such as 17α-hydroxyprogesterone, and androgens.

Report of a Case

A 22-year-old woman, diagnosed at birth as having CAH, had sudden visual loss in the right eye and pyramidal, sensory, and cerebellar signs.

Evidence of a congenital salt-wasting 21-hydroxylase deficiency consisted of ambiguous external genitalia, hyponatremia, hyperkalemia, and high levels of 17α-hydroxyprogesterone, corticotropin, and renin. Appropriate hydrocortisone and fludrocortisone treatment produced a good outcome. The CAH diagnosis was subsequently confirmed by the detection of a homozygote N172I mutation of the CYP21 gene on chromosome 6.

Five days after the onset of neurological symptoms, a magnetic resonance image showed several T2-hyperintense white...
matter lesions, located in periventricular areas, the corpus callosum, the pons, and the cerebellum. Visual evoked responses were absent in the right eye and delayed in the left eye. Visual symptoms, and visual evoked response abnormalities, were completely resolved after intravenous treatment with methylprednisolone, 1 g/d, for 3 days. Two years later, she had vertigo, nausea, and ataxia, which recovered spontaneously after 7 days. The magnetic resonance image showed additional demyelinating areas; some T1-weighted lesions were enhancing (Figure 1).

A cerebrospinal fluid examination revealed an elevated IgG index (2.00) and numerous oligoclonal bands at the isoelectric focusing. Four months later, she had left sixth cranial nerve impairment with diplopia, which resolved with corticosteroid treatment. Thereafter, her neurological status was completely stable. At the last neurological examination, September 13, 2003, she had only asymmetry of deep tendon reflexes and a mild tremor in her left arm.

**COMMENT**

The patient described herein fulfills the diagnostic criteria for CAH and relapsing-remitting multiple sclerosis (MS). Given that the report seems to be unique, it is possible that the 2 diseases are randomly associated. However, the following clues suggest that CAH and MS could share common determinants.

The CYP21 gene is located within the HLA complex locus on chromosome 6p21, which is one of the genetic regions related to MS susceptibility. In a previous study on MS patients, a significantly higher frequency of the C4AQ0 allele was reported in those with relapsing-remitting MS than in control subjects: 50% of C4AQ0-positive MS patients showed a structural deletion of the C4/CYP21 gene complex. The CYP21 gene and the CYP21P pseudogene alternate in tandem with the C4 genes, which code for the homonym complement protein (Figure 2).

Finally, magnetic resonance imaging focal areas of T2-increased signal intensity in the white matter, without corresponding to neurological impairment, were detected in 4 (27%) of 15 CAH patients by Sinforiani et al, in 14 (36%) of 39 patients by Nass et al, and in 7 (30%) of 23 patients by us (R.B., C.L., E.C., C.U., D.F., and V.C., unpublished data, 2003).

In these series, white matter abnormalities were diffuse (mostly periventricular) and focal. Diffuse white matter abnormalities could be an expression of hypotensive episodes, producing infarctions in watershed areas. A different explanation could be that they are the expression of myelin sufferance, interpretable as extrapontine myelinolysis, induced by the rapid correction of hyponatremia. Concerning focal white matter abnormalities, some of them, such as the lesions in the cerebellum and the corpus callosum (R.B., C.L., E.C., C.U., D.F., and V.C., unpublished data, 2003), are similar to those typical of MS.

Therefore, we can speculate that the co-occurrence of CAH and central nervous system demyelination could in fact be nonrandom. First, validation of this alternative hypothesis would depend on a plausible reason as...
to why the CAH-MS co-occurrence has been described in only one case and why all the previous CAH patients with white matter abnormalities, perhaps interpretable as demyelinating lesions, had no clinical neurological signs. A possible explanation derives from the interplay between MS-inducing immunopathological processes and the particular “hormonal environment” that characterizes CAH patients. These latter patients are indeed exposed before and after birth to high levels of dehydroepiandrosterone and progesterone, which can have anti-inflammatory effects and a protective role for myelin.7,8 The dual-signal hypothesis on MS pathogenesis holds that 2 concomitant (but possibly unrelated) inflammatory events, respectively occurring in the central nervous system and in the periphery, constitute the crucial elements in the disease’s development.9 Accordingly, in those CAH patients who are prone to develop MS, hormonal factors could modulate the peripheral MS-promoting autoimmune events and prevent these patients from exceeding the clinical threshold of the disease. In this scenario, the patients could show only mild pathological signs, not overt clinical manifestations.

Of course, the explanation of the relationships between MS and CAH can derive only from extensive epidemiological and genetic studies. However, our observation should alert neurologists to the presence of signs and symptoms suggestive of CAH in MS patients and, in turn, endocrinologists to the appearance of neurological signs and symptoms in CAH patients.

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REFERENCES