Original Article

Brain magnetic resonance imaging findings in adult patients with congenital adrenal hyperplasia: Increased frequency of white matter impairment and temporal lobe structures dysgenesis

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ABSTRACT

Background: Congenital adrenal hyperplasia (CAH) is an inherited recessive disorder of adrenal steroidogenesis. The enzymes most commonly affected are 21-hydroxylase. Past reports suggested brain magnetic resonance imaging (MRI) abnormalities in CAH patients, affecting white matter signal, temporal lobe and amygdala structure and function. **Aims:** In the present study, we aimed to investigate the frequency of white matter changes and temporal lobes structures dysgenesis in a population of patients having CAH due to 21-hydroxylase deficiency. **Materials and Methods:** Neurological examination and brain MRI were performed in 26 patients. **Results:** Neurological examination revealed mental retardation in three patients, tremor in two patients, tendon reflexes asymmetry in one patient, and cerebellar syndrome in one patient. Eleven patients (42.3%) showed MRI abnormalities: Eight of them had white matter hyperintensities, one patient had moderate atrophy in the right temporal, and hippocampal dysgenesis was found in the remaining two patients. **Conclusions:** Brain MRI abnormalities in CAH patients include white matter hyperintensities and temporal lobe structures dysgenesis. The mechanisms involved seem related to hormonal imbalances during brain development and exposure to excess exogenous glucocorticoids. Clinical implications of such lesions remain unclear. More extensive studies are required to define better the relationships between brain involvement and different CAH phenotypes and treatment regimens.

Key words: Congenital adrenal hyperplasia, glucocorticoids, leukoencephalopathy, magnetic resonance imaging, temporal lobe

Introduction

Congenital adrenal hyperplasia (CAH) describes a group of inherited autosomal recessive disorders that cause a deficiency in an adrenal enzyme resulting in altered cortisol and aldosterone secretion. The most frequent CAH variant, accounting for 95% of all affected patients, is 21-hydroxylase deficiency (21-OHD) and is caused by inactivating mutations in the 21-hydroxylase gene (CYP21A2). The deficiency of 21-hydroxylase causes a decrease in negative feedback to the hypothalamic-pituitary-adrenal (HPA) axis, and subsequent hyperplasia of the adrenal gland.[1,2] Cortisol and aldosterone precursors are subsequently diverted to androgens, causing increased virilization and a chronic hyperandrogenic state.[2] There are different clinical forms of CAH associated with 21-OHD: Classical CAH, the most severe form comprises both salt-wasting (SW) and simple virilizing (SV) forms, and the non-classical (NC) form which may be asymptomatic or associated with symptoms of postnatal or even adult onset hyperandrogenism.[1] The prevalence of classic 21-OHD is approximately 1 in 15,000 births in most populations.[3] Several

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studies have suggested high concordance rates between genotype and phenotype in patients with the classic form of CAH.[4] Treatment of CAH consists of replacement of glucocorticoids and, when necessary, mineralocorticoids to prevent adrenal crises and to suppress the abnormal secretion of androgens and steroid precursors from the adrenal cortex.[5,6] Conventional glucocorticoid replacement cannot, however, mimic the natural circadian rhythms of cortisol release. Even in adequately treated patients, there are reports of clinical evidence of both over-suppression with glucocorticoid including iatrogenic Cushing's syndrome, obesity, and decreasing growth velocity and under-suppression including virilization, menstrual disorders and infertility, growth suppression, and development of adrenal tumors.[4]

CAH constitutes an interesting natural model for studying interactions between hormones and the brain.[7] Until now, only a few studies described brain magnetic resonance imaging (MRI) abnormalities in CAH patients. These abnormalities affect white matter signal, temporal lobe and amygdala structure and function. Hormonal imbalances during early development and exposure to excess exogenous glucocorticoids are the most probable explanations for these MRI findings.[7-11]

In the present study, we investigated the frequency of white matter changes and temporal lobe structures dysgenesis in patients with CAH due to 21-OHD.

Materials and Methods

Subjects

We studied 26 patients with CAH due to 21-OHD (11 males and 15 females, mean age ± SD = 27.4 ± 8.2 years, range = 16.5-48 years), who were followed at the department of endocrinology in Mahdia and Sfax, in Tunisia. This sample includes all patients with CAH, aged more than 16 years and regularly followed at these two clinics since 1982. Clinical characterizations and MRI findings of the recruited patients are presented in Table 1. The diagnosis of CAH was based on clinical and biochemical criteria (i.e., elevated levels of 17-hydroxyprogesterone (17-OHP) and androstenedione, ACTH stimulation test). None of the patients was treated in utero with dexamethasone. Ten patients (6 M, 4 F) had the SW form of CAH. They had been diagnosed in their first year of life and had been treated, from the time of diagnosis, with glucocorticoids and mineralocorticoids. Eight patients (5 M, 3 F, age at diagnosis: Between birth and 6 years) were diagnosed as classical SV patients. In the other eight patients (women only in this group), the NC form was diagnosed between 15 and 44 years of age. Twenty-one patients were started on a regimen of hydrocortisone (HC), given 2 or 3 times daily, whereas the remaining five patients (three with the NC form and two with the classic SV form) were treated with dexamethasone (once daily). Salt wasters were treated with 27.9 ± 9.6 mg/m^2 per day of HC the first 2 years of life, and the doses were decreased to 17.6 ± 6.6 mg/m^2 per day during childhood. Daily doses of HC in patients with classical and NC forms were respectively, 17.3 ± 4.6 mg/m^2 and 16.04 ± 3.4 mg/m^2 during adulthood. For dexamethasone, the prescribed doses ranged from 0.25 to 0.75 mg/day. Fifteen patients additionally received 9α-fludrocortisone (FC; twice daily).

The adequacy of therapy was monitored periodically on the basis of clinical and laboratory data, in accordance with current guidelines.[12]

Patients were classified as under adequate hormonal control if 50% or more of the total serum androgen levels were within normal limits for age or if 50% or more of the baseline serum 17-OHP concentrations were 2.0-10 ng/mL (6-30 nmol/L). Possible overtreatment was defined as suppressed androgen and 17-OHP levels in serum.

The mean duration of the follow-up period was 18.5 ± 9.3 (range 3-41.5) years. Seven patients (five with the SW form and two with the SV form) had experienced a SW adrenal crisis in the neonatal period.

One female patient (patient no. 23) with the NC form had a history of previously diagnosed congenital hypothyroidism. She was started on L-thyroxine 10 μg/kg per day at the age of 6 months, but she was irregular in follow-up and was not compliant with treatment.

One patient (patient no. 4) with the SW form developed hypertension at 8 years of age and responded well to Nifedipine. Detailed investigations (renal Doppler ultrasound, adrenal CT scan, urinary metanephrine, 11-deoxycortisol, and aldosterone concentrations) failed to detect any cause for secondary hypertension, and a diagnosis of essential hypertension was made.

All our patients or their parents gave their informed consent to participate in the study and underwent neurological examination and brain MRI.

Methods

All patients underwent neurological and MRI examinations. The MRI examination was performed with a 1 T. Siemens Magnetom Impact system. The imaging protocol included axial and sagittal spin-echo (SE) T1-weighted [repetition time (TR) 550 ms, echo time (TE) 15 ms, flip angle 90°], axial and coronal enhanced T1-weighted (TR 550 ms, TE 15 ms, flip angle 90°, axial fast SE (FSE) T2-weighted (TR 5000 ms, TE 94 ms, flip angle 90°), axial proton-density

Table 1: Clinical and brain magnetic resonance imaging findings in 26 patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

Patient no./sex/age, years	Phenotype	Neurologic signs	Brain MRI signs		
			White matter hyperintensities	Temporal lobe structures dysgenesis	Other signs
1/M/21	SW	Tendon reflexes asymmetry	+(cerebellar)	-	-
2/M/18	SW	-	-	-	-
3/M/23	SW	-	-	-	-
4/M/16,5	SW	-Tremor -Cerebellarsyndrome -Mental retardation	+(periventricular)	-	-Cortico-subcortical atrophy -Agenesis of the corpus callosum
5/M/22,5	SW	-	-	-	-
6/M/22,5	SW	Mental retardation	+(periventricular)	-	-
7/M/31	SV	-	-	-	-
8/M/17,5	SV	-	-	-	-
9/M/18	SV	-	-	-	-
10/M/28	SV	-	+(periventricular)	-	-
11/M/47,5	SV	-	-	+(temporal lobe atrophy)	-
12/F/21	SV	-	-	-	-
13/F/26	SV	-	+(periventricular)	-	-
14/F/25	SW	-	-	-	-
15/F/23,5	SW	-	+(periventricular)	-	-
16/F/22	SW	-	-	-	-
17/F/27	SW	-	-	-	-
18/F/33	SV	-	+(periventricular)	-	-
19/F/28	NC	-	-	-	-
20/F/26	NC	-	-	-	-
21/F/30,5	NC	-	-	+(globular hippocampus)	-
22/F/48	NC	-	-	-	-
23/F/36	NC	Mental retardation	-	+(small hippocampus)	-
24/F/36	NC	-	-	-	-
25/F/34	NC	-	+(periventricular)	-	Empty sella
26/F/32	NC	-	-	-	-

SW: Salt-wasting, SV: Simple virilizing, NC: Non-classical, MRI: Magnetic resonance imaging

(PD) T2-weighted (TR 2500 ms, TE 18 ms, flip angle 90°), and coronal fluid-attenuated inversion recovery [FLAIR; TR 7500 ms, TE 94 ms, inversion time (TI) 2200, flip angle 90°] sections. Brain MRI abnormalities were evaluated by two experienced radiologists. White matter changes were defined as areas of increased signal intensity on intermediate and T2-weighted sequences. Thin coronal MRI slices, perpendicular to the axis of the hippocampus were used for determining hippocampal dysplasia (hippocampus with distorted anatomy, small volume, disturbed internal architecture, and increased signal on T2 and FLAIR images). Amygdala was regarded as dysplastic if it was smaller than the contralateral side, if increased signal on T2 and FLAIR sequences was observed, or both.

Further investigations, including viral serologies, amino acid profile, organic acid profile, lactate, ceruloplasmin, lumbar puncture and arylsulfatase A activity, were performed in a16.5-year-old patient (patient no. 4) with the classical SW form of CAH and who presented with hypertension, obesity, mental decline, tremor, cerebellar syndrome, white matter hyperintensities, and agenesis of the corpus callosum. All these investigations revealed negative or normal results.

Results

Clinical characteristics

On neurological examination, mental retardation was evident in three patients (patient nos. 4, 6 and 23). On intellectual quotient test, it was moderate in patient nos. 4 and 6 (both had developed salt losing crisis during the neonatal period) and profound in patient no. 23 (having poor control of congenital hypothyroidism). Other neurological signs included postural and action tremor in two patients (patient nos. 4 and 23), tendon reflexes asymmetry in one patient (patient no. 1), and static and kinetic cerebellar syndrome in one patient (patient no. 4).

Hormonal control

At the time of inclusion in the study, mean morning baseline 17-OHP in serum for the whole cohort was 22.51 ng/mL (range, 1.1-77); mean morning androstenedione levels were 5.25 ng/mL (range, 1.6-24) and mean morning plasma ACTH levels were 118.31 pg/mL (range, 6.5-537).

During the treatment period, nine patients (34.6%) showed well-controlled CAH. Poor hormonal control, with elevation

of 50% or more of Δ4-androstenedione and 17-OHP serum measurements, was present in 16 patients (61.5%). These were chronically non-compliant patients, mainly because of ignorance and lack of understanding. The remaining patient (patient no. 8) had suppressed androgen and 17-OHP levels indicating possible over-treatment.

Brain magnetic resonance imaging findings

Fifteen patients (57.7%) had normal brain MRI. Eleven patients (five males and six females, 42.3%) showed MRI abnormalities: One patient was over-treated (patient no. 8), two patients had good hormonal control (patient nos. 13 and 15) and eight patients were poorly controlled due to non-compliance with their medication. Eight patients (seven with the classic form and one with the NC form) evidenced white matter hyperintensities on T2-weighted and FLAIR images. These hyperintensities were located in periventricular regions in seven patients [Figure 1a] and in cerebellar white matter in the remaining patient [patient no. 1, Figure 2]. One patient (patient no. 11) with the classical SV form showed moderate right temporal lobe atrophy [Figure 3]. Indeed, two patients with the NC form showed right hippocampal dysgenesis: Patient no. 23 had small right hippocampus [Figure 4], whereas in patient no. 21, hippocampus was globular in shape and its internal structures were not identified [Figure 5]. Other MRI findings included partially empty sella in one patient (patient no. 25) and cortico-subcortical atrophy associated with complete agenesis of the corpus callosum in another patient [patient no. 4, Figure 1b]. No cases of amygdala atrophy were identified. Clinical and MRI findings are summarized in Table 1.

Discussion

Our study provides evidence of an increased frequency of white matter abnormalities and temporal lobe structures dysgenesis in CAH patients.

In the past, only a few studies described brain MRI abnormalities in CAH.[7-11] Table 2 summarizes the major results. Overall, these studies documented abnormalities affecting white matter signal, temporal lobe and amygdala structure and function.

White matter hyperintensities, or leukoencephalopathy, related to CAH are an interesting finding in this population. In a previous Italian study, leukoencephalopathy lesions were found in 10 (45%) of 22 cases with CAH.[7] Disease phenotype does not seem to affect the frequency of such lesions, which may even be present in heterozygous carriers of CYP21 mutations.[7,13]

Brain white matter impairment in CAH involve typically periventricular regions or, less frequently, cerebellar area as seen in one of our patients. These signal changes are non-specific and without side prevalence,[7-9] but they differ from those due to ischemic causes, as the latter involve namely subcortical and deep structures.[14]

White matter hyperintensities in CAH are most often subclinical or, less frequently, associated with unremarkable neurological signs.[8] In the present study, 3/26 patients revealed an abnormal neurological examination.

The data in the literature concerning the clinical significance of white matter lesions are controversial. It has been suggested that a "threshold" area of white matter lesions must be present before cognitive deficits are installed.[8]

The mechanisms that could explain MRI lesions in CAH remain poorly understood. Hormonal imbalance related to a deficiency of cortisol and aldosterone and an overproduction of 17-OH-progesterone and androgen would cause a destabilization of the myelin molecule leading to its degeneration.[7] In addition, exogenous

Table 2: Major previous reports of brain magnetic resonance imaging abnormalities related to congenital adrenal hyperplasia

References	Patients *n* (%)	Age (years)	Phenotype (*n*)	Neurologic signs	MRI findings
Sinforiani *et al.*[8]	4 (27)	>16	SW: 2/SV: 2	No	-Leukoencephalopathy -Cerebral atrophy -Ventricular dilatation
Nass *et al.*[9]	18 (46.1)	4-33	SW: 12/SV: 6	None except for one with known stroke	-Leukoencephalopathy -Cerebral atrophy
Merke *et al.*[10]	27 (100)*	6-16	SW: 18/SV: 9	No	Cerebral atrophy
Bergamashi *et al* [7]	10 (45)	16-23	SW: 6/SV: 4	No	Leukoencephalopathy
Gaudiano *et al.*[13]	3(A family)	27-54	Proband: CF Parents: heterozygous carriers	Yes	-Leukoencephalopathy -Cerebral atrophy -Ventricular dilatation
Present study	11 (42.3)	16.5-48	SW: 4/SV: 4 NC: 3	Yes	-Leukoencephalopathy -Hippocampal dysgenesis -Agenesis of the corpus callosum

%Percentage of patients with abnormal MRI in the study population. *Patients were compared to a control group. SW: Salt-wasting, SV: Simple virilizing, NC: Non-classical, CF: classical form, MRI: Magnetic resonance imaging

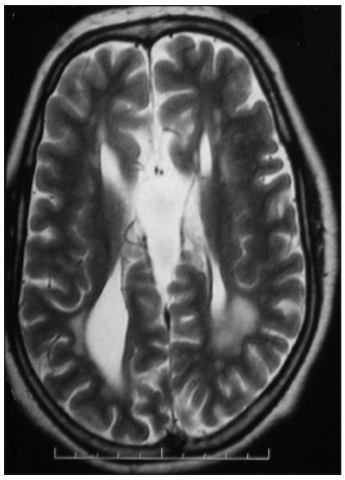

Figure 1a: T2-weighted axial MRI sequence showing bilateral periventricular white matter hyperintensities and cortico-subcortical atrophy in a 16.5-year-old patient affected by SWCAH (patient no. 4)

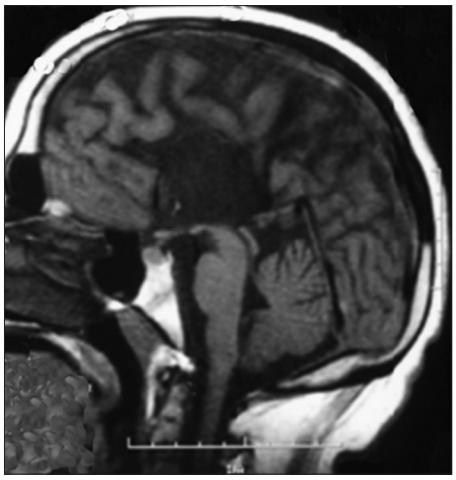

Figure 1b: T1-weighted sagittal MRI sequence showing complete agenesis of the corpus callosum in a 16.5-year-old patient affected by SWCAH (patient no. 4)

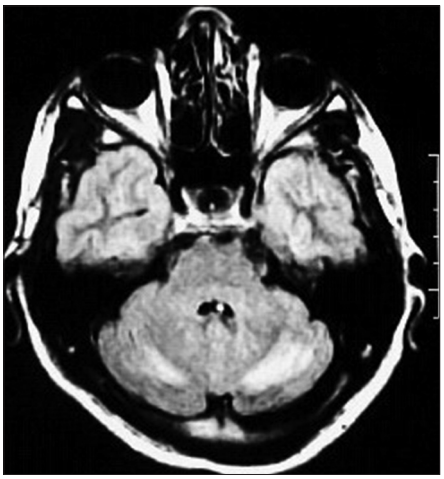

Figure 2: Axial flair and T2 MRI showing bilateral cerebellar white matter hyperintensities in a 21-year-old man affected by SW CAH (patient no. 1)

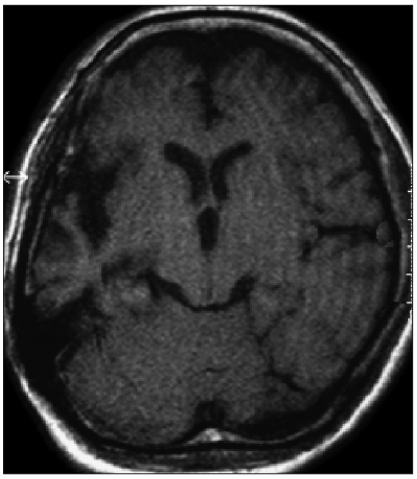

Figure 3: Axial T1-weighted image showing moderate atrophy in the right anterior temporal lobe in a 47.5-year-old man affected by simple virilizingCAH (patient no. 11)

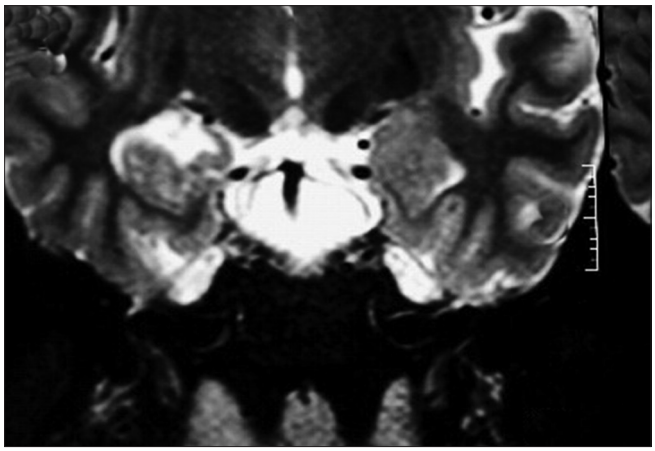

Figure 4: T2-weighted MRI, coronal section, showing right hippocampal atrophy in a 36-year-old woman affected by non-classic CAH (patient no. 23)

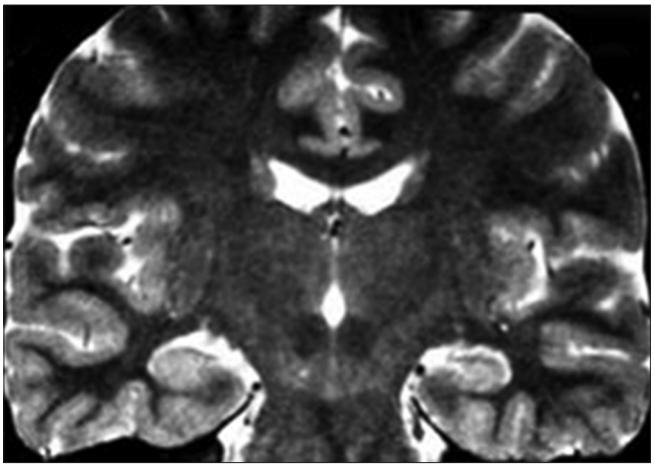

Figure 5: Coronal T2-weighted MRI in a 30.5-year-old woman affected by non-classic CAH. The right hippocampus is moderately round-shaped and its internal structures are not identified (patient no. 21)

glucocorticoids may alter the process of neuronal maturation and myelination by inhibiting the differentiation of oligodendrocyte precursors.[7] Thus both, overdose and discontinuous therapy have been suggested as factors favoring the emergence of brain MRI abnormalities.[8]

In our patients, chronic hyperandrogenism, a result of non-compliance with treatment, may be the main mechanism involved in the genesis of brain MRI abnormalities.

Aldosterone is provided with a regulating effect on the arterial structure by stimulating fibroblast proliferation and collagen synthesis via direct activation of local receptors. In this regard, aldosterone deficiency could induce changes of cerebral arterial structure, and, as consequence, a subclinical cerebral ischemia.[7] This ischemia could also be indirectly promoted by glucocorticoids that alter glucose and lipid metabolism and reduce platelet aggregability.[8]

In our study, one patient had cerebellar white matter abnormalities. Similarly, Nass, *et al.* reported some CAH patients with white matter lesions, with localizations that were typical of demyelinating diseases (located in the corpus callosum and cerebellum).[9] In addition, Bergamaschi, *et al.* have described a patient whose condition was diagnosed at birth as the SW subtype of CAH in whom relapsing-remitting multiple sclerosis developed.[15] The fact that a susceptibility locus for multiple sclerosis is in the HLA region that comprises the CYP21 genes suggests a possible genetic link between multiple sclerosis and CAH.[7,15]

Steroids can have two types of effects, organizational and activational effects. The organizational effects refer to permanent changes in brain structure, organization or function in utero or during critical periods of development. The activational effects tend to be transient and refer to the acute effects of circulating steroids during adulthood.[16] Two structures are known to have many androgen and glucocorticoid receptors and are particularly susceptible to the effects of excess glucocorticoids: The hippocampus, a central neural substrate of declarative memory, and the amygdala, a key to emotional coding. The hippocampus also plays an important role in the fine-tuning of the HPA axis by participating in its glucocorticoid negative feedback regulation.[11]

Alterations in amygdala function have been implicated in the pathophysiological characteristics of anxiety and depressive disorders in both adults and children.[10,17] The effect of hypercortisolism on the amygdala has not been systematically studied;[18] however, patients with classic CAH, who have prenatal glucocorticoid deficiency with possible postnatal iatrogenic glucocorticoid excess, have smaller amygdala volume than healthy age-and sex-matched controls.[10] CAH female patients have also enhanced response to negative facial emotions (anger and fear) compared with neutral expressions.[11]

Animal studies and human studies of adult patients with chronic hypercortisolemia have shown that prolonged exposure to glucocorticoid excess could result in extensive hippocampus damage and permanent memory impairment.[19] Cushing's disease is associated with brain atrophy and cognitive deficits. Excess glucocorticoids alter dendritic morphology of adult hippocampal formation and reduce its volume. The mechanisms leading to brain atrophy include impaired neurogenesis, reduction in neurotrophic factors and reduction in cerebral glucose metabolism. Interestingly, it has been suggested that at least some of the deleterious effects of prolonged hypercortisolemia on cognitive functioning and hippocampal volume are reversible.[18,20,21]

Our present study showed temporal lobe atrophy in one patient and hippocampal dysgenesis in two patients. This study is the first one demonstrating hippocampal abnormalities on MR imaging in patients with CAH, and it showed, also for the first time, brain MRI abnormalities in patients with the NC form of CAH.

Studies of cognitive function in CAH patients have reported discrepant findings. It was suggested that patients with the most severe form of CAH and those who have experienced SW adrenal crises with abnormal electrolytes as neonates are at risk for cognitive impairement.[22] In the present study, three patients showed mental decline. Two of them had the SW form. The remaining one had the NC form, but also had an uncontrolled congenital hypothyroidism which may also contribute to his altered mental status.

In conclusion, brain MRI abnormalities are an interesting finding in CAH patients and could affect white matter signal and temporal lobe structures. These abnormalities could be the consequence of hormonal imbalance during brain development and corticosteroid treatment. A possible genetic link with demyelinating diseases could also be considered. Clinical implications of such lesions remain unclear, but could precede cognitive dysfunction. More extensive studies are required to define better the relationships between brain involvement and different CAH phenotypes and treatment regimens.

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