

Editor's Comment: The authors pointed out the need for further testing in larger populations, as their study was not designed to establish predictive and/or pathogenic roles of APA. Nonetheless, this paper provides compelling data and a very plausible model that justifies pursuing this line of research. Endocrinologists certainly have precedent in using antibody titers to try to predict hormonal dysfunction and understand disease pathogenesis in disorders of the pancreas,^{1,2} adrenals,³ and thyroid.⁴ From a practical perspective, measuring APA titers is a far more appealing diagnostic test than the inaccessible pituitary biopsy, for both clinicians and

their patients in search of a diagnosis, with the default option of an "idiopathic" non-diagnosis. Hopefully, APA testing will be available to clinicians soon.

Adda Grimberg, MD

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Impaired Cognitive Function in Congenital Adrenal Hyperplasia

Cognitive function in individuals with congenital adrenal hyperplasia (CAH) is a topic of considerable interest. Effects of the condition or its treatment on cognitive function are plausible, ie, a permanent influence of sex steroid hormones *in utero* on brain development, the genetics of CAH or allied alleles, or the effects of under- or over-treatment with glucocorticoids during early postnatal period. Johannsen and colleagues conducted a case-control study of cognitive function in adult women with CAH. Participants included 35 women (84% of the eligible sample) diagnosed with CAH between 1953 and 2003 at a university hospital in Denmark. The patients with CYP21 mutations were grouped into salt wasters (SWs; n = 19, mean age, 31.2 yr; range, 19–46 yr), simple virilizers (SVs; n = 6, 34.6 yr, 23–51), late-onset (LO) CAH (n = 5, 25.5 yr, 19–36) and a mixed group of patients (mixed; n = 5, 28.8 yr, 17–49) with steroidogenic acute regulatory protein (StAR) deficiency (n = 3), CYP21 deficiency diagnosed in adolescence (n = 1), and 17-hydroxylase deficiency (n = 1). Patients with CYP21

deficiency were categorized by mutation severity, salt-wasting status, and clinical presentation. Control group participants were recruited through a general population registry of women born in the same month and year as the patient (response rate = 38%). The woman with the closest match on education was selected for pair-wise matching with the index patient. All participants received a medical interview, physical examination, psychological interview, cognitive assessment, hormone analyses and personality, sexual, and social functioning questionnaires. Five subtests (3 of 6 Verbal and 2 of 5 Performance) from the Wechsler Adult Intelligence Scale (WAIS) provided 3 indices of intelligence (IQ): full-scale IQs (FSIQ), performance (PIQ), and verbal (VIQ). (WAIS IQ scores are defined to yield a population mean of 100 [SD = 15].) Examiners were not blinded with respect to patients' diagnoses.

The combined CAH patient group achieved significantly lower FSIQ (84.5 vs 99.1), VIQ (86.6 vs 97.3) and PIQ scores (85.7 vs 101.3) than the pair-matched control group (Table). The same pattern was true for the

SW subgroup. The LO patients also achieved significantly lower FSIQ and VIQ scores than matched controls. Further, the mixed group received significantly lower scores than controls on all IQ indices. In contrast, the SV subgroup was not statistically different from control participants. The SW group received significantly lower FSIQ and VIQ than the SV group, and a nonsignificant trend was observed for PIQ. Patients with verified hyponatremic crises (n = 14) vs all other CAH patients (n = 21) revealed significantly lower FSIQ (78.6 vs 88.4) and VIQ (79.9 vs 91.0), but not PIQ (82.9 vs 87.6).

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Full-scale, verbal, and performance IQs in patients with CAH and matched controls.

	n	Full-scale IQ [mean ± SEM (range)]	Verbal IQ [mean ± SEM (range)]	Performance IQ [mean ± SEM (range)]
All CAH patients	35	84.5 ± 2.1 (62–114) ^a	86.6 ± 2.0 (64–107) ^a	85.7 ± 2.4 (62–127) ^a
All controls	35	99.1 ± 2.1 (67–133)	97.3 ± 2.1 (70–132)	101.3 ± 2.0 (73–122)
Salt-wasting CAH	19	81.2 ± 3.2 (62–114) ^b	84.7 ± 2.8 (66–107) ^b	81.5 ± 3.6 (62–127) ^a
Salt-wasting CAH controls	19	96.5 ± 2.6 (67–113)	95.4 ± 2.8 (70–115)	99.1 ± 2.7 (73–120)
Simple-virilizing CAH	6	92.8 ± 2.9 (83–103)	95.5 ± 3.6 (84–103)	91.3 ± 5.1 (73–105)
Simple-virilizing CAH controls	6	95.7 ± 3.6 (85–110)	92.7 ± 2.0 (86–101)	100.0 ± 5.4 (84–120)
LO CAH	5	91.6 ± 4.0 (79–104) ^b	90.0 ± 3.6 (78–99) ^b	96.2 ± 4.0 (87–110)
LO CAH controls	5	105.6 ± 5.6 (92–124)	104.6 ± 4.4 (94–119)	105.0 ± 5.6 (91–122)
Mixed CAH ^c	5	80.0 ± 3.7 (67–88) ^p	79.4 ± 4.7 (64–90) ^p	84.8 ± 2.9 (78–92) ^p
Mixed CAH ^c controls	5	106.2 ± 7.7 (92–133)	102.6 ± 8.5 (85–132)	107.8 ± 4.1 (99–122)

Significance levels for differences between patients and matched controls are indicated as ^a P < 0.001 or ^b P < 0.05.

^c Mixed CAH: three patients with StAR deficiency, one patient with 210H deficiency diagnosed in adolescence, and one patient with 17OH deficiency.

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Johanssen TH, Ripa CPL, Reinisch JM, Schwartz M, Mortensen EL, Main KM. Impaired cognitive function in women with congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2006;91:1376–1381.

Editor's Comment: Pediatric endocrinologists have traditionally been taught that cognitive function and IQ in patients with CAH are not usually sources of concern. This study, and others,^{1,2} suggest the contrary: individuals with CAH, particularly the SW-variant, are at risk for lower IQ. Elevated prenatal androgen exposure may affect later patterns of cognitive development and cerebral lateralization, thus individuals with CAH may exhibit a male-typical pattern of cognitive strengths and hemispheric lateralization,^{3–5} although other research challenges this conclusion.⁶

This paper underscores the importance of partitioning the sample in data analyses according to genetic mutation and clinical sequelae. In particular, those individuals who had suffered multiple hyponatremic episodes should be considered a particularly high-risk group for neuropsychological sequelae. Although these investigators grouped CAH participants into categories according to corticosteroid replacement dose, it is puzzling that accompanying analyses were not reported. Nevertheless, the authors noted that glucocorticoids are important for normal maturation of the developing central nervous system and that excessive doses in infancy (reduced in current treatment recommendations⁷) might be partially responsible for the pattern of intellectual

deficits observed in this cohort.

This study and corroborating findings underscore the importance of surveilling cognitive function among children born with CAH. To this condition, one could add Turner, Noonan, and Klinefelter syndromes, congenital hypothyroidism, children born small for gestational age, early-onset diabetes, and many others who frequent pediatric endocrinology clinics. Forging collaborations between pediatric endocrinology and hospital-based pediatric psychology or child psychiatry programs that can offer neuropsychological evaluations would likely spare many youths (and their families) needless academic failure and frustration.

David E. Sandberg, PhD

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Imprinting, Transcription Factories, and Igf2 Regulation

An important regulator of fetal growth, insulin-like growth factor 2 (Igf2), has received much attention in recent years because it is imprinted, ie, expressed only from the paternal allele, in contrast to the Igf2 receptor, which is expressed only from the maternal allele. New clues regarding regulation of *Igf2* expression have emerged as further insight is gained into how gene expression is

regulated in general and how DNA and chromosomes are organized in the nucleus.

As commented upon by Spilnakis and Flavell, DNA in higher organisms is organized with nucleoproteins into different kinds of chromatin from which chromosomes are constructed. Each chromosome resides in a specific region of the nucleus except during cell division.