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Clinical Study

Normal Intelligence in Female and Male Patients with Congenital Adrenal Hyperplasia

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We provide evidence regarding the nature, causes, and consequences of intelligence in patients with 21-hydroxylase deficient congenital adrenal hyperplasia (CAH). Intelligence and quality of life (psychological adjustment) were measured on multiple occasions from childhood to young adulthood in 104 patients with CAH (62 females, 42 males) and 88 unaffected relatives (31 females, 57 males). Information on disease severity (CAH type, age at diagnosis, genital virilization for girls) and salt-wasting crises was obtained from medical records. There was no evidence of intellectual deficit in either female or male patients with CAH. Intelligence was not significantly associated with psychological adjustment or disease characteristics. CAH itself does not appear to increase risk for poor intellectual function. In a sample of patients with generally good disease control, intelligence is not related to adjustment problems, disease severity, or salt-wasting crises.

1. Introduction

Controversies about the nature and causes of psychological outcome in individuals with disorders of sex development (DSDs) have focused on gender identity, sexuality (especially related to surgery), and quality of life [1–3]. There has been less attention paid to intelligence, although there has been a concern that intellectual impairment might be associated with adjustment problems [4]. Most of the systematic evidence about outcome in DSDs comes from congenital adrenal hyperplasia (CAH), the most common DSD.

Intelligence is composed of several key attributes, including abstract thinking, reasoning, problem-solving, and ability to adapt to the environment [5]. Intelligence measured by standard tests is important because it is associated with a variety of psychological, social, economic, and health outcomes [5]. A review of studies through 2000 indicated that overall intelligence of individuals with CAH is within the normal range, but might be lower in patients with salt-wasting (SW) than with simple-virilizing (SV) CAH [6]. One aspect of intelligence, spatial ability, has been found to be affected by CAH, but in different ways in the two sexes: compared to same-sex controls, females with CAH have higher spatial ability (probably as a result of prenatal androgen excess) and males have lower spatial ability (for unknown reasons) [6–8]. Data published since the review suggest that there is a more pronounced intellectual deficit in female patients with CAH than had been reported previously [4]. The deficit was proposed to be caused by the disease and its treatment (e.g., prenatal androgen excess, hyponatremia) and to lead to lowered quality of life, but the hypothesized causes and consequences of the deficit were not tested.

The renewed concerns about intellectual deficits in CAH and associations with psychological adjustment [4] generate three key questions. First, what is the nature and extent of the deficit, and is it found in both sexes? Although most work focuses on females with CAH, some factors proposed to influence intelligence (e.g., hyponatremia) are also present in males with CAH. Second, what are the causes of intellectual deficit? This can be examined through associations between

intelligence and disease characteristics. Third, what are the psychological consequences of intellectual deficit? This can be examined through associations between intelligence and psychological adjustment. We address these questions with data from a long-term followup of individuals with CAH whose intelligence and psychological adjustment were assessed on multiple occasions from childhood through young adulthood.

2. Methods

2.1. Subjects. Participants were part of a behavioral study of individuals with CAH secondary to 21-hydroxylase deficiency studied on several occasions. They were initially recruited in childhood or adolescence through eight university-affiliated pediatric endocrinology clinics in the midwestern United States. Unaffected relatives similar in age served as controls. Participants represented a range of socioeconomic backgrounds, and most were Caucasian. There were 192 participants from 90 families studied at several points between the ages of 3 and 30 years, although not all subjects had data at all times; there were 62 females and 42 males with CAH, 31 unaffected female relatives (29 sisters, 2 cousins) and 57 unaffected male relatives (54 brothers, 3 cousins). 90% of families invited to participate in the project agreed.

Behavioral data from some participants have been reported; for summary, see [1, 9]. In brief, females with classical CAH are behaviorally more male-typical and less female-typical than their unaffected sisters, with androgen having large effects on activity interests but minimal effects on gender identity; males with classical CAH are similar to unaffected males in gender-related characteristics studied; females and males with CAH have good psychological adjustment.

The research was approved by Institutional Review Boards at all institutions. Depending on age, participants provided oral assent or written consent; parents of minors provided written consent for their children's participation.

2.2. Measures and Procedures. Subjects were tested between one and four times between 1989 and 2004. At the initial assessment (Time 1), they ranged in age from 3 to 13 years ($M = 6.9$), but cognitive testing was only conducted on those aged 7 and older ($M = 9.5$). Subsequent assessments included both the initial subjects and new subjects, and included cognitive tests for all subjects. The second assessment (Time 2) occurred on average six months after the first, and subjects were 3 to 13 years old ($M = 8.10$). The third assessment (Time 3) occurred on average 4.6 years later, and subjects were 3 to 19 years old ($M = 10.33$). The final assessment (Time 4) occurred on average 5.6 years after that, and subjects were 9 to 30 years old ($M = 15.87$). Most participants were tested more than once: 33% had only one assessment, 43% had two, 16% had three, and 8% had all four assessments.

Intelligence was measured with standardized tests. Raven's Progressive Matrices Test was administered at Time 1; it correlates well with other measures of intelligence [10]. Peabody Picture Vocabulary Test [11] was administered at Times 2 and 3. Age-appropriate multiple-choice Vocabulary Tests [12, 13] were administered at Time 4. Vocabulary tests were used because they correlate with measures of intelligence [11] but are short (reducing participant burden), and prevent inflated scores in females with CAH who have higher spatial ability than unaffected females [8] and depressed scores in males with CAH who have lower spatial ability than unaffected males [6, 7].

Psychological adjustment was measured with parent-report on all four occasions, and with self-report once or twice in adolescence. Parents completed the Child Behavior Checklist (ages 3–18) or the Young Adult Behavior Checklist (age 18 and older) [14, 15]; analyses focused on Internalizing (withdrawal, somatic complaints, depression, and anxiety), Externalizing (aggressive and delinquent behavior), and Total Behavior Problem scales. Adolescents completed the Self-Image Questionnaire for Young Adolescents [16]; an average of all nine scales was used. Some adjustment data have been reported [17] so only associations with intelligence are described.

Disease characteristics that might affect intelligence were rated from medical records without knowledge of behavioral results. Data were available for approximately half the sample; there were no significant behavioral differences between those with versus without data. The overwhelming majority of patients were diagnosed clinically, consistent with the fact that most were born before newborn screening for CAH was implemented in the states in which they lived. Most participants had good disease control, as measured by growth rate, bone age, and concentration of 17-hydroxyprogesterone; see [18] for detailed information about assessment and results. Measures used here include indicators of disease severity (type of CAH, age at diagnosis, degree of genital virilization in girls) and number of salt-wasting crises documented in childhood; descriptive data are shown in Table 1. Type of CAH was classified as simple virilizing (SV-), mild salt wasting (SW-), or severe SW. SW-CAH required elevated plasma renin activity for age and responsiveness to mineralocorticoid therapy. Classification as mild SW-CAH required that all measurements of serum sodium be at least 129 mmol/L, and that there be no episodes of hypotension or shock; classification as severe SW-CAH required that serum sodium in the neonatal period be less than 129 mmol/L, or that there be at least one episode of hypotension or shock.

2.3. Analysis Procedure. Intelligence test scores of patients and controls were compared using analysis of variance, with factors of sex and status (CAH, control), and covariate of age for tests that were not age-standardized. Separate analyses were conducted for each measure at each time point; multivariate analyses were not used because not all subjects had complete data. Associations between intelligence and adjustment were assessed with correlations; scores were adjusted so positive correlations reflect high intelligence associated with good adjustment. We examined correlations

Table 1: Disease characteristics of patients with CAH.

Type of CAH	Females	Males		
Nonclassical (NC)	7	6		
Simple Virilizing (SV)	6	2		
Mild Salt-Wasting (Mild SW)	11	8		
Severe Salt-Wasting (Severe SW)	31	24		
Age at Diagnosis of CAH	Females	Males		
<6 months	38	27		
6–35 months	3	0		
>36 months	12	11		
Prader Stage at Diagnosis (females only)	NC	SV	Mild SW	Severe SW
0	6	2	0	0
1	1	1	2	1
2	0	1	3	3
3	0	1	1	12
4	0	1	3	11
Number of Salt-Wasting Crises (SW-CAH only)	Females	Males		
0	29	23		
1	9	6		
2	4	3		

Note. Entries are numbers of subjects. Some participants do not have complete data, so total numbers vary across characteristics.

of intelligence to adjustment at the same point in time, and at earlier and later times, in order to assess time-lagged consequences of intelligence for adjustment and vice versa. Associations between intelligence and disease characteristics were also assessed with correlations. Because of the importance of detecting problems if they are present, Type I error was set at .05 and there were no corrections for multiple tests; increased Type I error with multiple comparisons is discussed later.

3. Results

3.1. Group Comparisons on Intelligence. Data on intelligence test scores and test ages for females and males with and without CAH at all assessments are shown in Table 2. There was no evidence of intellectual deficit in either females or males with CAH at any assessment. There was one significant effect of status, reflecting higher scores of patients with CAH than controls at Time 2 ($P < .05$). This effect was qualified by a marginally significant interaction between sex and status ($P < .07$): higher scores of patients with CAH than controls were specific to females. An interaction between sex and status was also seen at Time 3 ($P < .01$), again reflecting the higher scores of females, but not males, with CAH compared to controls.

3.2. Associations between Intelligence and Adjustment. Intelligence was generally not significantly associated with adjustment, whether measured at the same or different points in time. Only a few correlations were significant, and they were not consistently in the same direction. The median correlation was −.02.

3.3. Associations between Intelligence and Disease Characteristics. Intelligence was generally not significantly associated with disease characteristics. Median correlations with intelligence were as follows: type of CAH $r = .12$, age at diagnosis $r = -.07$, Prader rating $r = .01$, number of salt-wasting crises $r = -.05$. Because few patients had more than one salt-wasting crisis, we compared individuals with one or more crisis to individuals with no crises; t-tests showed no significant group differences on any measure of intelligence.

4. Discussion

Across multiple measures and assessments, there was no evidence that patients with CAH—female or male—had impaired intelligence. If anything, females with CAH had higher ability than unaffected female relatives. Further, there was no evidence that intelligence was associated with quality of life, as measured by parents' reports of their children's behavior problems or patients' reports of their own functioning, and no evidence that intelligence was associated with disease characteristics, including salt-wasting crises. Published data from this sample show that the disease was well-controlled in the majority of patients [18], which might account for their favorable outcome; restricted variability might also account for lack of association between intelligence and salt-wasting crises.

These results are consistent with the bulk of the data on intelligence in CAH from several countries and cohorts, as seen in a review [6] and recent studies [7, 19, 20]. Patients with CAH are consistently seen to have normal intelligence. Intelligence may be somewhat lower in patients with SW-CAH than SV-CAH but both groups are within the normal range and there is variability within groups [6, 21].

Table 2: Intelligence test scores and age at test by sex and status (CAH, control).

	Females with CAH	Unaffected Females	Males with CAH	Unaffected Males	Significant Effects
Time 1, Progressive Matrices [10]: Number correct of 36					
N	14	9	9	16	
Mean	30.71	25.33	28.22	27.81	
SD	4.80	8.32	4.12	4.68	
Age at test (years)					
Mean	10.68	8.85	8.95	9.21	
SD	1.09	1.30	1.58	1.47	
Time 2, Peabody Picture Vocabulary Test [11]: Standardized Score					
N	18	13	18	19	
Mean	105.33	92.15	102.56	101.79	F CAH>Unaff^{+}
SD	15.87	18.52	12.72	13.97	
Age at test (years)					
Mean	8.51	8.14	7.42	8.34	
SD	3.33	1.54	2.66	2.49	
Time 3, Peabody Picture Vocabulary Test [11]: Standardized Score					
N	45	25	30	42	
Mean	110.56	101.16	107.01	106.95	F CAH>Unaff*
SD	13.24	15.17	12.59	15.49	
Age at test (years)					
Mean	10.43	10.57	9.64	10.57	
SD	4.17	4.80	3.76	3.51	
Time 4, Vocabulary [12, 13] Percent correct[a]					
N	44	18	29	31	
Mean	0.72	0.62	0.61	0.71	
SD	0.17	0.24	0.20	0.16	
Age at test (years)					
Mean	15.71	16.76	15.76	15.66	
SD	4.99	4.28	5.07	3.61	

[a]Because of variability in participant age, several different forms of this test were used. To increase the statistical power to detect group differences, scores were combined into a single Vocabulary measure.
Most group differences are not significant. Significant effects are noted, $^{+}P < .07$, $^{*}P < .01$.

Impairments may be associated with repeated hyponatremic episodes. There is a greater likelihood of deficits in patients who are not well-treated [4] than in those who are (as in the current study), but one or two episodes in otherwise well-treated patients do not appear to have adverse consequences for intelligence. Intellectual deficits might also result from other disease features, although this has not been tested. For example, elevated ACTH with undertreatment might lead to attention problems; overtreatment with glucocorticoids might lead to cognitive and neural changes similar to those seen in Cushing syndrome [22].

Our findings of enhanced ability on some tests in females with CAH most likely reflect sampling fluctuation. If intelligence does not differ in populations of people with versus without CAH, then sampling fluctuations in individual studies may produce varying group differences, including higher ability in CAH than in controls (as found here), lower ability in CAH than in controls (as found by [4, 23]) and, most often, no significant group differences in ability [7, 19, 20, 24–28]. Group differences in intelligence are less likely to be seen when patients are compared to siblings (the best control for genetic and environmental influences on intelligence) than to unrelated controls.

Our results showing few links between intelligence and adjustment are consistent with findings in typical samples [29]. Links may be found in a narrow context (e.g., intelligence correlated with the personality dimension of Openness), or in selected groups (e.g., mentally ill, unusually high or low ability), but overall, adjustment and ability are not highly correlated.

Several issues bear consideration in interpreting the results. First, intelligence was not assessed with full IQ tests, such as Wechsler scales. But the tests used correlate well with Verbal and Full Scale IQ, and are considered good indicators of general intelligence [10, 11]. Second, conclusions about associations between intelligence and disease characteristics

must be tempered by the methods of assessment and the nature of the sample: medical information was rated retrospectively from medical records that varied in quality, and most patients had good disease control as reported elsewhere [18]. Although medical data were not available for all participants, those with and without data were similar in intelligence and adjustment. It is important to emphasize that findings of normal intelligence in these patients mean that there is little need for explanatory medical data. Third, the sample is large enough to detect moderate-to-large differences between patients with CAH and unaffected relatives; small differences are unlikely to be of clinical significance. Indeed, there was enough power to detect a difference, but it was of an intelligence advantage (not deficit) in females with CAH. The sample was also large enough to detect moderate-to-large associations between intelligence and adjustment and between intelligence and disease characteristics. Fourth, Type I error was very high in light of the many comparisons made. It is thus particularly noteworthy that significant effects were not found. Fifth, the patients studied likely represent the population of patients with CAH, given that most individuals contacted agreed to participate; this increases confidence that most patients with CAH are intellectually similar to their unaffected relatives. Nevertheless, it is important to examine intelligence in patients with CAH detected through newborn screening, who best represent the population of patients with CAH.

5. Conclusions

Results of systematic assessment show that intelligence is not impaired in females or males with CAH who generally received good medical care beginning early in life, and that ability is not associated with psychological adjustment. This conclusion is strengthened by the consistency of findings across repeated assessments with multiple measures. It seems unlikely that CAH itself causes cognitive deficits.

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References

[1] S. A. Berenbaum, "Psychological outcome in children with disorders of sex development: Implications for treatment and understanding typical development," *Annual Review of Sex Research*, vol. 17, pp. 1–38, 2006.

[2] P. E. Clayton, W. L. Miller, S. E. Oberfield et al., "Consensus statement on 21-hydroxylase deficiency from the Lawson Wilkins Pediatric Endocrine Society and The European Society for Pediatric Endocrinology," *Journal of Clinical Endocrinology and Metabolism*, vol. 87, no. 9, pp. 4048–4053, 2002.

[3] I. A. Hughes, C. Houk, S. F. Ahmed, P. A. Lee, and LWPES/ESPE Consensus Group, "Consensus statement on management of intersex disorders," *Archives of Disease in Childhood*, vol. 91, no. 7, pp. 554–563, 2006.

[4] T. H. Johannsen, C. P. L. Ripa, J. M. Reinisch, M. Schwartz, E. L. Mortensen, and K. M. Main, "Impaired cognitive function in women with congenital adrenal hyperplasia," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 4, pp. 1376–1381, 2006.

[5] J. M. Sattler, *Assessment of Children*, Jerome M. Sattler, La Mesa, Calif, USA, 5th edition, 2008.

[6] S. A. Berenbaum, "Cognitive function in congenital adrenal hyperplasia," *Endocrinology and Metabolism Clinics of North America*, vol. 30, no. 1, pp. 173–192, 2001.

[7] M. Hines, B. A. Fane, V. L. Pasterski, G. A. Mathews, G. S. Conway, and C. Brook, "Spatial abilities following prenatal androgen abnormality: targeting and mental rotations performance in individuals with congenital adrenal hyperplasia," *Psychoneuroendocrinology*, vol. 28, no. 8, pp. 1010–1026, 2003.

[8] D. A. Puts, M. A. McDaniel, C. L. Jordan, and S. M. Breedlove, "Spatial ability and prenatal androgens: meta-analyses of congenital adrenal hyperplasia and digit ratio (2D:4D) studies," *Archives of Sexual Behavior*, vol. 37, no. 1, pp. 100–111, 2008.

[9] S. A. Berenbaum, "Androgen and behavior: implications for the treatment of children with disorders of sexual differentiation," in *Pediatric Endocrinology: Mechanisms, Manifestations, and Management*, O. H. Pescovitz and E. A. Eugster, Eds., pp. 275–284, Lippincott Williams & Wilkins, Philadelphia, Pa, USA, 2004.

[10] J. C. Raven, *Standard Progressive Matrices*, Psychological Corporation, New York, NY, USA, 1958.

[11] L. M. Dunn and L. M. Dunn, *Peabody Picture Vocabulary Test: Revised Manual for Forms L and M*, American Guidance Service, Circle Pines, Minn, USA, 1981.

[12] R. B. Ekstrom, J. W. French, and H. H. Harman, *Kit of Factor-Referenced Cognitive Tests*, Educational Testing Service, Princeton, NJ, USA, 1976.

[13] T. Thurstone, *Primary Mental Abilities Tests*, Science Research Associates, Chicago, Ill, USA, 1963.

[14] T. M. Achenbach and L. A. Rescorla, *Manual for ASEBA School-Age Forms & Profiles*, Research Center for Children, Youth, & Families, University of Vermont, Burlington, Vt, USA, 2001.

[15] T. M. Achenbach and L. A. Rescorla, *Manual for the ASEBA Adult Forms & Profiles*, Research Center for Children, Youth, & Families, University of Vermont, Burlington, Vt, USA, 2003.

[16] A. C. Petersen, J. E. Schulenberg, R. H. Abramowitz, D. Offer, and H. D. Jarcho, "A self-image questionnaire for young adolescents (SIQYA): reliability and validity studies," *Journal of Youth and Adolescence*, vol. 13, no. 2, pp. 93–111, 1984.

[17] S. A. Berenbaum, K. K. Bryk, S. C. Duck, and S. M. Resnick, "Psychological adjustment in children and adults with congenital adrenal hyperplasia," *Journal of Pediatrics*, vol. 144, no. 6, pp. 741–746, 2004.

[18] S. A. Berenbaum, S. C. Duck, and K. Bryk, "Behavioral effects of prenatal versus postnatal androgen excess in children with 21-hydroxylase-deficient congenital adrenal hyperplasia," *Journal of Clinical Endocrinology and Metabolism*, vol. 85, no. 2, pp. 727–733, 2000.

[19] W. M. Kelso, M. E. R. Nicholls, G. L. Warne, and M. Zacharin, "Cerebral lateralization and cognitive functioning in patients with congenital adrenal hyperplasia," *Neuropsychology*, vol. 14, no. 3, pp. 370–378, 2000.

[20] M. A. Malouf, C. J. Migeon, K. A. Carson, L. Petrucci, and A. B. Wisniewski, "Cognitive outcome in adult women affected by congenital adrenal hyperplasia due to 21-hydroxylase deficiency," *Hormone Research*, vol. 65, no. 3, pp. 142–150, 2006.

[21] S. C. Mueller, V. Temple, E. Oh et al., "Early androgen exposure modulates spatial cognition in congenital adrenal hyperplasia," *Psychoneuroendocrinology*, vol. 33, no. 7, pp. 973–980, 2008.

[22] I. Bourdeau, C. Bard, H. Forget, Y. Boulanger, H. Cohen, and A. Lacroix, "Cognitive function and cerebral assessment in patients who have Cushing's syndrome," *Endocrinology and Metabolism Clinics of North America*, vol. 34, no. 2, pp. 357–369, 2005.

[23] J. Helleday, A. Bartfai, E. M. Ritzen, and M. Forsman, "General intelligence and cognitive profile in women with congenital adrenal hyperplasia," *Psychoneuroendocrinology*, vol. 19, no. 4, pp. 343–356, 1994.

[24] S. W. Baker and A. A. Ehrhardt, "Prenatal androgen, intelligence, and cognitive sex differences," in *Sex Differences in Behavior*, R. C. Friedman, R. M. Richart, and R. L. Vande Wiele, Eds., John Wiley & Sons, New York, NY, USA, 1974.

[25] V. G. Lewis, J. Money, and R. Epstein, "Concordance of verbal and nonverbal ability in the adrenogenital syndrome," *Johns Hopkins Medical Journal*, vol. 122, no. 4, pp. 192–195, 1968.

[26] L. S. McGuire and G. S. Omenn, "Congenital adrenal hyperplasia. I. Family studies of IQ," *Behavior Genetics*, vol. 5, no. 2, pp. 165–173, 1975.

[27] S. M. Resnick, *Psychological functioning in individuals with congenital adrenal hyperplasia: early hormonal influences on cognition and personality*, Ph.D. thesis, University of Minnesota, Minneapolis, Minn, USA, 1982.

[28] U. Wenzel, M. Schneider, M. Zachmann, G. Knorr-Murset, A. Weber, and A. Prader, "Intelligence of patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency, their parents and unaffected siblings," *Helvetica Paediatrica Acta*, vol. 33, no. 1, pp. 11–16, 1978.

[29] M. Zeidner and G. Matthews, "Intelligence and personality," in *Handbook of Intelligence*, R. J. Sternberg, Ed., pp. 581–610, Cambridge University Press, New York, NY, USA, 2000.