Psychoneuroendocrinology (2015) 54, 60—70

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/psyneuen

Spatial function in adolescents and young adults with congenital adrenal hyperplasia: Clinical phenotype and implications for the androgen hypothesis

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Received 6 October 2014; received in revised form 25 January 2015; accepted 26 January 2015

KEYWORDS
Congenital adrenal hyperplasia;
21-Hydroxylase deficiency;
Androgen;
Cognitive;
Spatial

Summary Females with the classic form of congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency are said to perform better than unaffected female controls on tests of mental rotation or other visuospatial abilities, but findings are conflicting. We studied 31 adolescents and young adults with CAH and 19 unaffected sibling controls, who were given standardized spatial tests and tests of other sexually differentiated cognitive functions (verbal fluency, perceptual speed). The possible role of CAH subtype (salt-wasting or simple-virilizing) was evaluated. Only females with the more severe, salt-wasting form of CAH, but not females with the simple-virilizing form, performed significantly better than sex-matched sibling controls on measures of mental rotation. Subtype differences were not significant for verbal fluency or perceptual speed. Severity of prenatal genital virilization, but not postnatal age when medication was started, predicted accuracy on the Mental Rotations Test. Results are consistent with the possibility of an organizational effect of androgens in the central nervous system that impacts the development of spatial abilities. Implications for the timing of the hypothetical critical period are discussed.

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a rare disorder of the adrenal cortex in which production of androgens is elevated, beginning in the 3rd month of gestation (New, 1998). In females, the most obvious effect is genital virilization, which varies in severity. If

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http://dx.doi.org/10.1016/j.psyneuen.2015.01.022
0306-4530/

CAH is diagnosed in the newborn and glucocorticoid therapy is promptly begun, the androgen excess can be confined to the prenatal period and first week or two of life. Females typically undergo surgical repair of the ambiguous genitalia in infancy and are raised as girls. Genital morphology is unaffected in males with CAH, whose upbringing is male-typical.

Ambiguous genital morphology is the most visible sign of CAH in females. However, in other species exposure to testosterone or its metabolites during early development organizes regions of the central nervous system (CNS) into a male-typical pattern (Breedlove and Hampson, 2002). Whether the human CNS is subject to the organizational effects of androgens is controversial. Consistent with this possibility, girls with CAH show increased preference for boys as childhood playmates and for boys' toys and activities (Nordenström et al., 2002) despite parental encouragement of the female gender role (Pasterski et al., 2005), and as adults may show altered patterns of sexual orientation (Meyer-Bahlburg et al., 2008).

The cognitive profile of females with CAH is of considerable interest in light of neuroendocrine theories speculating that the organizational effects of sex steroids may extend to cognitive processes (Collaer and Hines, 1995). Certain spatial abilities, particularly mental rotation (the ability to visualize the rotation of an object around its axis), show a reliable male advantage in the general population (Voyer et al., 1995) and elements of the sex difference can be identified in infants <6 months of age (Moore and Johnson, 2008; Quinn and Liben, 2008). The capacity of androgens to modify spatially relevant regions of the CNS in laboratory animals (Isgor and Sengelaub, 2003) supports the possibility that spatial function in humans too is organized by androgens. A few studies have reported superior performance by females with CAH relative to controls on mental rotation tasks, figural disembedding, or learning the layout of a virtual environment (Resnick et al., 1986; Hampson et al., 1998; Mueller et al., 2008; Berenbaum et al., 2012), but these data are controversial because other studies have failed to find an effect on spatial abilities (Baker and Ehrhardt, 1974; McGuire et al., 1975; Helleday et al., 1994) or have even found *lower* scores in CAH samples (Perlman, 1973). Hines et al. (2003) reported that females with CAH outperformed unaffected female relatives on throwing projectiles at targets, but showed no difference on tests of mental rotation. Arguing against a prenatal effect, Hines suggested that if androgens do influence the development of cortical regions mediating mental rotation their influence is likely to be postnatal, perhaps coinciding with the rise in testosterone seen in normally developing males during the first 6 months of life.

A recent meta-analysis concluded that existing evidence favors an effect of CAH on spatial cognition, but lamented the mixed state of the literature (Puts et al., 2008). Mixed findings are partly attributable to measurement issues including unsuitable tasks in older studies. However, the importance of disease-related variables, particularly the form of CAH, has seldom been investigated.

CAH is expressed in two phenotypic forms. Both involve elevated exposure to androgens in utero. In approximately 67% of cases, children have a concomitant deficit in aldosterone production (Merke and Bornstein, 2005), resulting in excessive sodium excretion in the urine. This is known as 'salt-wasting' CAH (SW). In contrast, the other 33% display simple virilization only, or 'simple-virilizing' CAH (SV). Some individuals, especially males, who have the simple-virilizing form escape detection until inappropriate signs of virilization become evident in childhood. Delayed detection means a longer period of postnatal androgen excess. The salt-wasting variant is associated on average with greater androgen production by the adrenals (Therrell et al., 1998), therefore the biochemical anomaly and degree of genital virilization is usually more severe than in the simple-virilizing form. Patients with salt-wasting require mineralocorticoid replacement in addition to glucocorticoid therapy to prevent electrolyte imbalance, vascular collapse, and death due to excessive sodium loss. In jurisdictions where CAH is detected through clinical ascertainment instead of newborn screening, there is increased morbidity and mortality due to loss of sodium homeostasis in infants with the salt-wasting form of the disorder.

The issue of subtype has received negligible attention in the context of spatial function. The two studies that currently exist have produced conflicting findings. Specifically, Malouf et al. (2006) found no difference between salt-wasters and simple-virilizers on a mental rotation test. In a younger sample, Mueller et al. (2008) found that females with salt-wasting showed latencies similar to male controls on a spatial learning task, whereas females with simple-virilizing CAH resembled female controls.

Patient neurological status too could be an important determinant of cognitive outcomes in CAH, but has been overlooked by most studies. Although not well-documented, diminished cognitive function is observed in a subset of children who experienced early salt-wasting crises (Johannsen et al., 2006). Reports of lower mean IQs in salt-wasting than simple-virilizing groups due to a few very low-scoring individuals (Nass and Baker, 1991a,b; Helleday et al., 1994) suggest the phenomenon may be more prevalent than often recognized. If present, impaired IQ associated with neurological complications could mask any improvement in spatial ability attributable to androgens because performance on many spatial tasks is influenced by general intelligence not just spatial ability.

The purpose of the present study was to investigate spatial function in a clinically ascertained sample of patients with CAH. We explored whether CAH subtype moderates the magnitude of the spatial effect. We additionally sought to explore the moderating role of neurological status. It was predicted that neurologically intact females with CAH would show superior performance compared with unaffected female controls. Superior spatial function was expected only in females because males with CAH do not have reliably higher testosterone in utero than male controls (Forest, 1985; Wudy et al., 1999). If Hines et al. (2003) are correct and it is androgen exposure *post*natally not prenatally that is important, then enhanced spatial ability should be seen predominately among females with simple-virilizing CAH, whose diagnosis and treatment is often delayed resulting in androgen excess extending into infancy or early childhood.