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SPATIAL ABILITY IN ANDROGEN-DEFICIENT MEN

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Abstract Several lines of previous evidence have suggested that androgens affect cognitive abilities. In an effort to characterize this defect, we compared 19 men with idiopathic hypogonadotropic hypogonadism with 19 control men and with five men with acquired hypergonadotropic hypogonadism that had developed after puberty. The 19 patients with idiopathic hypogonadism had markedly impaired spatial ability in comparison to either controls or subjects with acquired hypogonadism ($P < 0.05$). Moreover, the spatial ability of the patients cor-

related positively with their testicular volume ($P < 0.05$). Androgen-replacement therapy in six of the patients did not improve their spatial ability.

The impairment in spatial ability in men with the idiopathic form of hypogonadotropic hypogonadism, the lack of such an impairment in men with the acquired form, and the failure of exogenous androgens to correct the deficits in the idiopathic form suggest that androgens exert a permanent organizing influence on the brain before or at puberty in boys. (*N Engl J Med.* 1982; 306:1202-5.)

THE mammalian brain possesses both neuronal receptors for the gonadal steroids and enzymes suitable for their metabolism.^{1,2} Although the gonadal steroids have been shown to alter brain structure in the regions relevant to sexual behavior,³⁻⁵ the influence of these steroids on other brain regions remains uncertain. Similarly, although gonadal steroids have been shown to influence reproductive behavior, their influence on human cognitive behavior remains largely conjectural.⁶

There are several reasons to suspect that the gonadal steroids may influence certain cognitive skills: first of all, there are striking sex differences in the prevalence of a variety of developmental language disorders, including dyslexia, delayed speech acquisition, stuttering, and infantile autism⁷; secondly, sex differences can be demonstrated for a variety of cognitive skills, with women generally faring better on verbal measures and men performing better on spatial and mathematical measures⁸; thirdly, these sex differences do not generally emerge until after puberty; fourthly, there

may be subtle sex differences in the interhemispheric organization of verbal and spatial abilities within the brain⁹; and finally, there appear to be sex differences in the pattern of cognitive deficits that occur after cerebral injury.¹⁰

Men with idiopathic hypogonadotropic hypogonadism constitute a unique group in which to examine the effect of profound androgen deficiency at puberty on the development of human cognitive skills. These men have a normal 46,XY karyotype; their masculinization occurs normally (or nearly normally) in utero, presumably under the influence of maternal gonadotropins; and they are reared and educated as normal boys until puberty, when pubescence fails to occur because of a presumptive deficiency in gonadotropin-releasing factor. Extensive testing of both hypothalamic and pituitary functioning in cases of idiopathic hypogonadotropic hypogonadism has generally shown an isolated deficiency of gonadotropin-releasing factor without evidence of other hypothalamic deficiencies.^{11,12} Neuropathological studies of idiopathic hypogonadotropic hypogonadism have not revealed major cerebral malformations except for agenesis of olfactory lobes in patients with anosmia.^{11,13} Furthermore, a disabling psychopathologic disturbance is not characteristic of idiopathic hypogonadotropic hypogonadism.¹⁴ Thus, idiopathic hypogonadotropic hypogonadism offers an opportunity to evaluate the effects of severe pubertal androgen deficiency on the development of human cognitive skills in the presence of minimal confounding influences of culture, education, cerebral injury, chromosomal aberrations, psychopathology, and non-gonadal endocrine disturb-

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ances. As such the disorder represents an almost ideal “experiment of nature” in which to examine the effects of androgen deficiency on cognitive function.

METHODS

Nineteen healthy men (mean age, 28.7 years), 19 men with idiopathic hypogonadotropic hypogonadism (mean age, 32.2 years), and five men with acquired hypogonadotropic hypogonadism (mean age, 30.5 years) were studied.

The 19 men with idiopathic hypogonadotropic hypogonadism met the following criteria: a 46,XY karyotype, a history of not undergoing puberty by the age of 18, a eunuchoid habitus, a normal roentgenogram of the sella turcica, small testes (less than 15 ml), and defective virilization before treatment. Four of the men with idiopathic hypogonadotropic hypogonadism had anosmia and thus fulfilled the diagnostic criteria for Kallmann’s syndrome.¹¹ After androgen-replacement therapy had been withdrawn for at least three months, all men with idiopathic hypogonadotropic hypogonadism had plasma and urinary gonadotropin levels below the normal male range and plasma testosterone levels within the female range (30 to 100 ng per deciliter). Base-line levels of growth hormone, ACTH, prolactin, and thyrotropin were normal in each patient. In addition, each patient had a normal response to reserve testing of these pituitary hormones by intravenous injection of insulin and thyrotropin-releasing factor.¹⁵

In the five men with acquired hypogonadotropic hypogonadism, the hypogonadism had developed during or after an otherwise normal puberty. All had plasma testosterone levels in the female range, plasma and urine gonadotropin levels below the normal male range, and a 46,XY karyotype. Three of the men with acquired hypogonadotropic hypogonadism had craniopharyngiomas. In the fourth man hypogonadotropic hypogonadism had developed after a serious head injury. In the fifth man, the cause was hemochromatosis.

Psychometric testing was performed in a single test session lasting for 90 minutes. Three tests of verbal ability and three tests of spatial ability were administered. The verbal tests were the Vocabulary, Similarities, and Information subtests from the Wechsler Adult Intelligence Scale.¹⁶ The spatial-ability tests were the Block Design subtest from the Wechsler Adult Intelligence test, the Embedded Figures Test,¹⁷ and the Space Relations subtest from the Differential Aptitude Tests.¹⁸

Statistical analyses, including linear regression, one-way analysis of variance, two-tailed t-tests, and analysis of variance of repeated measures, were performed with the BMDP Statistical Package.¹⁹

RESULTS

The three groups of subjects did not differ significantly in performance on any of the three tests of verbal ability, but on each of the three tests of spatial ability, the group with idiopathic hypogonadotropic hypogonadism differed significantly from the other groups (Table 1). An examination by t-tests of the group means revealed that the men with idiopathic hypogonadotropic hypogonadism did less well than the control men on all three tests of spatial ability ($P < 0.05$, $df = 36$), whereas the performance of the men with acquired hypogonadotropic hypogonadism did not differ significantly from that of the control men on any of these tests ($P > 0.05$, $df = 22$).

Testicular volume in the 19 men with idiopathic hypogonadotropic hypogonadism was measured with a Prader orchidometer. Volume per testis among these men ranged from a low of 1 ml to a high of 12 ml. Correlation coefficients were calculated between mean testicular volume and scores on the six psychometric tests (Table 2). Negligible correlations were found be-

Table 1. Mean Psychometric-Test Scores in the Three Groups and Results of Analysis of Variance.*

| TEST | IHH (N = 19) | CONTROLS (N = 19) | AHH (N = 5) | F † |
|--------------------|-----------------|----------------------|----------------|-------|
| Verbal ability | | | | |
| Similarities | 12.2 | 13.8 | 12.8 | 2.0 |
| Vocabulary | 12.5 | 13.5 | 13.6 | 2.0 |
| Information | 12.3 | 13.3 | 14.4 | 1.4 |
| Spatial ability | | | | |
| Block Design | 9.8 | 12.8 | 13.6 | 5.9 ‡ |
| Space Relations | 26.8 | 38.2 | 36.8 | 4.3 ‡ |
| Embedded Figures § | 69.8 sec | 37.4 sec | 37.8 sec | 6.6 ‡ |

*IHH denotes idiopathic hypogonadotropic hypogonadism, and AHH acquired hypogonadotropic hypogonadism.

†One-way analysis of variance, $df = 2,40$.

‡ $P < 0.05$.

§On the Embedded Figures Test, faster times reflect better performance.

tween scores on verbal tests and testicular volume. However, on both the Block Design and the Embedded Figures tests, larger testicular size correlated positively with better test performance ($P < 0.05$).

The effect of hormone-replacement therapy on spatial ability was studied in six of the men with the idiopathic disorder. After treatment with androgen-replacement therapy for at least three months, the three tests of spatial ability were readministered. Results were analyzed by a one-way analysis of variance (repeated-measures design), thus increasing the likelihood of detecting an improvement in test performance with androgen treatment. Nonetheless, even though there was no attempt to compensate for the probable effects of practice, there was no significant improvement in performance on any of the tests of spatial ability after hormone-replacement therapy (Table 3). Because of the small size of the sample, a small but significant improvement in test scores with androgen treatment cannot be excluded.

DISCUSSION

The 19 men with idiopathic hypogonadotropic hypogonadism had impaired spatial ability in comparison to men with normal gonadal function (Table 1). Furthermore, there appeared to be a direct relation between the severity of the idiopathic hypogonadotropic hypogonadism and the severity of the deficit in spatial ability. Among the men with the idiopathic hypogonadotropic hypogonadism, testicular volume was found to correlate significantly with performance on two of three tests of spatial ability (Table 2). Previous clinical studies have suggested that the degree of idiopathic hypogonadotropic hypogonadism may range from mild to severe, with larger testicular volumes correlating with higher endogenous levels of gonadotropins, gonadotropin-releasing hormone, and testosterone.^{20,21} Since testicular enlargement depends on the presence of gonadotropins, it is likely that the men with smaller testicular volumes had a more severe form of idiopathic hypogonadotropic hypogonadism. Thus, men with more severe forms of this disorder tend

Table 2. Correlation Coefficients between Testicular Volumes and Psychometric-Test Scores in 19 Men with Idiopathic Hypogonadotropic Hypogonadism.

| TEST | CORRELATION COEFFICIENT |
|------------------|-------------------------|
| Verbal ability | |
| Vocabulary | 0.08 |
| Information | 0.26 |
| Similarities | 0.10 |
| Spatial ability | |
| Block Design | 0.47 * |
| Space Relations | 0.37 |
| Embedded Figures | -0.51 † |

*Larger testicular volumes correlated positively with higher scores on the Block Design Test ($P < 0.05$, $df = 17$, two-tailed t -test).

†Larger testicular volumes correlated positively with faster times (better performance) on the Embedded Figures Test ($P < 0.05$, $df = 17$, two-tailed t -test).

to have lower spatial ability than men with milder forms.

Our results suggest that androgenization (presumably mediated by testosterone or one of its metabolites) is essential to the full development of spatial ability. Several other endocrine syndromes also suggest a link between androgenization and spatial ability. Men with androgen insensitivity (testicular feminization) have a 46,XY karyotype and a cellular defect in the testosterone receptor. Consequently, they have no manifestations of androgenization despite normal male levels of circulating testosterone. Such patients have low performance IQs suggestive of impaired spatial ability.^{22,23} However, interpretation of their deficit in spatial ability is somewhat difficult, since children with testicular feminization are generally reared as females and thus face cultural and educational sex biases. Similarly, women with Turner's syndrome (gonadal dysgenesis) have low levels of estrogens and androgens as a result of streak gonads.²⁴ These women have a marked deficit in spatial ability.^{25,26} Prepubertal boys with poor androgenization secondary to the liver disease of kwashiorkor syndrome also have an impairment in spatial ability.²⁷ Consistent with our observation of impaired spatial ability in men with idiopathic hypogonadotropic hypogonadism, Bobrow et al.¹⁴ have noted low performance IQs in seven men with Kallmann's syndrome.¹⁴ Buchsbaum and Henkin²⁸ found that six men with hypogonadotropic hypogonadism did poorly on the rod-and-frame test — a test that correlates well with spatial ability. However, it is of interest to note that mild degrees of hypogonadism are not associated with defective spatial ability. Men with Klinefelter's syndrome experience moderate hypogonadism secondary to partial gonadal failure,²⁹ yet have no special difficulties in spatial ability.^{26,30}

Our results also suggest that the influence of androgens on spatial ability is exerted at or before puberty. The development of hypogonadotropic hypogonadism after puberty was not associated with a deficit in spatial ability (Table 1). Once established, spatial skills do not appear to wane with falling levels of androgens. Furthermore, correction of the androgen deficiency in

six of the men with idiopathic hypogonadotropic hypogonadism did not result in a statistically significant improvement in spatial ability, indicating that this deficit had become fixed (Table 3). These observations suggest that some minimal level of androgens must be present before or at the time of puberty for spatial ability to develop fully and that replacement of androgens after puberty cannot compensate for an earlier deficiency in these hormones. In many ways, the situation in men with idiopathic hypogonadotropic hypogonadism may be analogous to the development of singing behavior in certain bird species. Male finches sing, whereas females do not. Moreover, adult female finches will not sing even when treated with testosterone if it is administered after sexual maturation. However, if the brain of the female finch is masculinized soon after hatching, the vocal areas in her brain enlarge to the male size, and she will then sing as an adult if treated with androgens.³¹ Thus, in finches androgens can influence outward behavior during adult life, but only if the proper brain substrate has developed after a carefully timed exposure to sex hormones in early life.

Although it seems parsimonious to attribute the impaired spatial ability of men with idiopathic hypogonadotropic hypogonadism to the effects of androgen deficiency on the brain, one cannot exclude the possibility of androgen-independent brain defects in these men because of the lack of detailed neuroanatomical studies.^{11,13} Determination of the extent and nature of the brain abnormalities in men with this disorder will require further neuroanatomical study.

The mechanism by which androgen deficiency may lead to an impairment in spatial ability in men with idiopathic hypogonadotropic hypogonadism is uncertain. Testosterone has been shown to have transient and reversible effects on central-nervous-system neuronal electrical activity.^{32,33} Testosterone also appears to exert permanent organizing effects on the structure of the central nervous system.^{3-5,34,35} The absence of these organizing influences as a result of androgen deficiency before or at puberty may cause a fixed deficit in spatial ability that cannot be corrected by later administration of exogenous androgens. On the other hand, the onset of profound hypogonadism after puberty (and after these putative organizing effects have been exerted) produces no apparent defect in spatial ability.

Table 3. Effect of Androgen-Replacement Therapy on Spatial Ability in Six Men with Idiopathic Hypogonadotropic Hypogonadism.

| TEST | OFF ANDROGENS * | ON ANDROGENS * | F † | P VALUE |
|------------------|-----------------|-----------------|-----|---------|
| Space Relations | 26.0 ± 18.3 | 28.5 ± 17.7 | 0.5 | 0.51 |
| Block Design | 10.0 ± 4.9 | 9.8 ± 4.8 | 0.1 | 0.77 |
| Embedded Figures | 58.3 ± 38.6 sec | 49.0 ± 42.6 sec | 3.9 | 0.10 |

*Values denote mean test scores ± S.D.

†Analysis of variance, repeated measures design, $df = 1,5$.

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MEDICAL PROGRESS

EVOKED POTENTIALS IN CLINICAL MEDICINE

(Second of Two Parts)

KEITH H. CHIAPPA, M.D., AND ALLAN H. ROPPER, M.D.

SHORT-LATENCY SOMATOSENSORY EVOKED POTENTIALS

Short-latency somatosensory evoked potentials (EPs) are recorded after stimulation of peripheral sensory nerves. They are functionally similar to brain-stem auditory EPs in that there is a close relation between wave forms and the anatomy of sensory tracts, allowing precise localization of conduction defects. Since the paths involved in short-latency somatosensory EPs traverse a greater extent of the central

nervous system than do those of brain-stem auditory EPs, they are of greater clinical utility. Cell bodies of the large-fiber sensory system lie in the dorsal-root ganglia; their central processes travel rostrally in ipsilateral posterior columns of the spinal cord and synapse in the dorsal-column nuclei at the cervicomedullary junction. Second-order fibers cross to the opposite side shortly after origination and travel to the thalamus through the medial lemniscus. Third-order fibers continue from the thalamus to the frontoparietal sensorimotor cortex.

Methods of Recording

Stimuli such as finger tapping^{157,158} and muscle stretching¹⁵⁹ produce short-latency somatosensory EPs, but electrical stimulation is commonly used be-

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