

SEX HORMONE TREATMENT AND SPATIAL ABILITY IN WOMEN WITH TURNER'S SYNDROME

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SUMMARY

Women with Turner's syndrome (probands) received a battery of tests of spatial ability. Some of the probands had been treated with estrogen for either a short time (<2 years) or a long time (>2 years). The tests were also administered to the probands' normal sisters who served as a control group. Spatial ability was below normal in both untreated and long-term treated probands, while the spatial ability of short-term treated probands was similar to that of their normal sisters. The results suggest that estrogen may influence neural structures and thereby affect the expression of spatial ability in women with Turner's syndrome. The results also suggest that spatial ability may be a sex-limited trait rather than a sex-linked trait. Some clinical implications of cyclical estrogen therapy are discussed and the need for further studies on possible effects of estrogen on higher mental functions is emphasized.

INTRODUCTION

In 1938 Turner¹ described a syndrome in individuals by the triad: 1. Short stature with undeveloped secondary sexual characteristics. 2. Webbing of the neck. 3. Cubitus valgus. The only one of these signs which is invariably present is short stature - rarely exceeding 1.55 m. Thus Nielsen, Nyborg and Dahl² found an average body height in individuals with Turner's syndrome of 1.46 m while webbing of the neck and cubitus valgus was observed in approximately 30 per cent and 60 per cent of the cases, respectively. Approximately half of the women with Turner's syndrome have karyotype 45,X. The other half comprises

women with a great variation of different X-chromosome aberrations. However, all lack some X-chromosome material.

Women with Turner's syndrome have been subjected to a number of studies by researchers from various disciplines for therapeutic as well as for theoretical reasons. Most of these studies have recently been reviewed by Nielsen et al.² One persistent finding in the psychological literature was that although full-scale IQ was found to be within normal limits, performance IQ was significantly depressed making it advisable to consider the verbal and the performance IQ scales separately for women with Turner's syndrome and not to rely upon the full-scale IQ. Even within the performance IQ-scale it seemed advisable to consider the sub-test scores separately as Buckley³ noted that Object assembly score was significantly lower in women with Turner's syndrome than those achieved on all other performance sub-tests including Block design.

Of special interest in the present context was the fact that women with Turner's syndrome (in the following synonymously called probands) obtained lower than expected scores in all those performance sub-test areas known to be highly correlated with spatial ability. In order to learn more about this specific deficit Nielsen et al.² tested 45 probands with a number of spatial tasks and compared their scores to those of carefully selected control groups. The probands demonstrated remarkably low spatial ability in all tests. Despite persistent efforts it was not possible to find a satisfactory explanation to this observation. Thus the depression of spatial ability did not reflect a given abnormal karyotype directly as probands with karyotype 45,X obtained the same low spatial ability score as did probands with other karyotypes. Furthermore, neither (a) presence of Y-chromosome material; (b) birth weight; (c) birth length; (d) pterygium colli; (e) cubitus valgus; (f) level of behavioral activity; (g) overprotective behavior of the mothers; (h) special difficulties in certain school subjects; (i) skeletal retardation; (j) 8/12 years mean growth-retardation; nor (k) retarded stature at time of testing, provided any convincing clue to why the probands performed so badly on spatial ability tests.

The question of the origin of spatial ability has also been

the concern of many developmental psychologists studying groups of normal girls and boys. The results have been puzzling and have hitherto escaped a complete explanation. It was for example found that boys were superior to girls but only after puberty, that boys identifying themselves as "feminine" had higher spatial ability scores than boys identifying themselves as "masculine" while conversely "masculine" girls were superior to "feminine" girls. This cross-sex pattern also showed up when body maturation rather than gender identity was used to classify subjects (for review see 4, 5). As sex hormones guides body maturation and relates to gender identity as well the above mentioned observations might indicate a relation between sex hormones and spatial ability. This possibility was further pursued in the present study of a hormonal abnormal population.

Women with Turner's syndrome lack the usual secondary sexual characteristics. Although they have female external genitalia the uterus and fallopian tubes remain of infantile size. Typically the gonads are rudimentary and are called "streak gonads". Such gonads are unable to produce the normal amount of the female sex hormone, estrogen. Their dysfunction is responsible for the absent development of secondary sexual characteristics including the usual lack of spontaneously appearing menstruation. However, in a few cases spontaneous menstruation may occur for a short period of time. The defective endogenous production of estrogen was compensated for in a number of our probands by means of exogenously administered cyclic estrogen-gestagen hormone treatment for various periods of time. This differential treatment with estrogen to inherently estrogen-low individuals provided a pseudo-experimental situation for testing if estrogen therapy might influence spatial ability.

Our first hypothesis was that probands treated with estrogen would obtain a higher spatial ability score than probands not treated. The result was negative as the two groups obtained practically identical scores. Our second hypothesis was that due to a more adequate compensation for the underproduction of estrogen the long-term treated group (>2 years) would obtain a higher spatial ability score than would the short-term treated group (<2 years). The observations ran directly counter to this ex-

pectation. These results indicated that the relation - if any - between estrogen and spatial ability was not understandable in terms of a simple linear model.

That a relation between sex hormones and spatial ability in fact exists was clearly enough indicated by the studies on normal girls and boys previously cited, and was further elaborated upon by Waber⁶. Furthermore, Klaiber et al.⁷ were able to demonstrate that spatial ability - as measured by the rod-and-frame task - cycled systematically with the menstrual cycle in normal women. Klaiber suggested that the observed systematic variation in spatial ability could be explained by menstrual changes in estrogen, causing changes in plasma monoamine oxidase (MAO) activity which in turn was believed to influence central nervous system adrenergic functioning. The theory has been severely criticized^{8,9}. The observation remains, however, that rising levels of plasma estrogen coincided with low spatial ability while decreasing levels of plasma estrogen coincided with high spatial ability. Finally, Dawson^{10,11} demonstrated that rats treated with estrogen made many more errors in a maze-learning situation (believed to reflect a spatial ability component). In summary these studies supported the idea of a relationship between estrogen and spatial ability, although the exact form of the relationship remained to be established.

The present study was therefore devoted to a more detailed study of this relationship in women with Turner's syndrome. The spatial ability and non-verbal school performance of women with Turner's syndrome was considered with respect to whether they received estrogen treatment and the length of treatment. It was anticipated that this approach would provide new information about the applicability of estrogen therapy to treat abnormal low spatial ability and would serve to set out guidelines for the administration of estrogen therapy.

METHOD

1. Subjects.

Thirty-four women with Turner's syndrome (probands) were studied. Their ages ranged from 15 to 38 years. Fourteen of the

chromosome abnormalities with lack of some X material in all or part of their cells as described by Nielsen et al.². The probands were divided into three groups according to length of hormone treatment received. 10 had received no estrogen treatment, 7 had received treatment for less than 2 years (short-term treatment), and 17 had received treatment for more than 2 years (long-term treatment). The total group of probands cannot be considered as an unselected group, because a larger than expected number of these girls lived in Copenhagen, while a smaller than expected number of the others lived in smaller towns and rural districts of Denmark.

Eighteen of the probands had sisters that were less than 5 years younger or older than themselves. These 18 sisters consented to be studied and served as the normal control group.

Test, instruments and procedure.

Spatial ability was measured individually by the Rod-and-Frame test (RFT), by the Embedded-Figures test (EFT), by the Human Figures-Drawing test (HFDT), and by Money's Road-Map test of direction sense (MRMT). Details about these tests and about the procedure can be found in Nyborg and Nielsen¹². In addition the subjects were tested by the Porteus Mazes test (PMT), and the degree of difficulty each woman encountered in mathematics and related school subjects (DAM) was estimated.

The Porteus Mazes test (PMT) consists of a number of roadmap-like diagrams. The subject was told that the lines could be considered as solid stone walls, which were not to be crossed, and to imagine that she was driving a car through the streets, from the entrance, through the maze, to the exit. If a blind alley was entered, it was forbidden to back or reverse the imaginary car (in the form of a pencil with which a line was traced), and it was forbidden to lift the pencil until the exit was reached. There was no time limit. Other rules of procedure and for calculating the quantitative and the qualitative score were as described by Porteus¹³.

Special difficulties in school with arithmetic and mathematics (DAM) were studied by interviewing the subjects, their parents, and their teachers. The school subjects were classified as pre-

TABLE 2

GROUP MEAN SCORES ON MONEY'S "ROAD-MAP TEST OF DIRECTION SENSE" (MRMT), DIFFICULTIES IN ARITHMETIC AND MATHEMATICS (DAM), AND ON PORTEUS MAZES TEST (PMT) FOR PROBANDS WITH (1) NO ESTROGEN, (2) SHORT-TERM CYCLIC ESTROGEN TREATMENT, (3) LONG-TERM CYCLIC ESTROGEN TREATMENT, AND (4) SISTERS

Group	MRMT		DAM		Porteus Mazes test (PMT)				
	N	Means	SD	Mean	SD	Mean	SD	Mean	SD
(1) No hormone	(10)	7.60 ^a	6.92	1.75 ^c	1.39	44.60	30.23	90.30 ^e	18.86
(2) Short-term treatment	(7)	2.00	1.63	2.71	1.60	44.14	29.12	101.86	14.09
(3) Long-term treatment	(17)	5.35 ^b	4.85	1.94 ^d	1.44	37.82	25.46	90.71 ^f	18.76
(4) Sisters	(18)	1.78	4.69	3.06	1.44	33.06	25.32	110.83	10.14

Probands:

- ^a Significantly different from group 2, $t(15) = 2.33$, $\underline{p} = .034$, and from group 4, $t(26) = -2.72$, $\underline{p} = .012$
^b Significantly different from group 2, $t(22) = -4.24$, $\underline{p} = .000$, and from group 4, $t(33) = -2.22$, $\underline{p} = .033$
^c Significantly different from group 4, $t(22) = 2.13$, $\underline{p} = .044$
^d Significantly different from group 4, $t(30) = 2.22$, $\underline{p} = .034$
^e Significantly different from group 4, $t(11:96) = 3.20$, $\underline{p} = .008$
^f Significantly different from group 4, $t(24:31) = 3.92$, $\underline{p} = .001$

NOTE: In case of inhomogeneous variance, separate variance estimates were calculated, as can be seen in fractionated D.f.'s.

senting special difficulties for the probands or their sisters only if most sources indicated such difficulties. The degree of difficulty was scaled from 1 to 4, with a score of four signifying no difficulties.

RESULTS

Table 1 shows the results of the studies carried out with the RFT, EFT and HFDT. Probands that had received either no hormone treatment or long-term treatment made significantly more errors than their sisters on these tests. In contrast, probands that had received short-term estrogen treatment made significantly fewer errors than the other two groups of probands and failed to differ significantly from the normal control group on these tests. Short-term treated probands tended to be less consistent in their responses in the RFT in that they had higher σ scores than either the other groups of probands or the control group, but these differences were not statistically significant.

Table 2 shows the results obtained with the MRMT, DAM and PMT. In general, the same pattern of results was found with these tests as with the other tests. Probands that had received either no hormone treatment or long-term treatment made significantly more errors than the control group on the MRMT and obtained lower scores on the DAM, while the MRMT and DAM scores of the short-term treated probands were within the normal range. The only exception to this pattern was found in the PMT. Probands that had received either no hormone treatment or long-term treatment made significantly fewer qualitative errors than the control group, while the scores obtained by short-term treated probands were within the normal range. The quantitative scores obtained in the PMT by the three groups of probands did not differ significantly from those of the control group.

DISCUSSION

Probands receiving no correction for their estrogen deficit have an abnormally low adult level of plasma estrogen. The data in Table 1 and 2 indicated that this condition might be related to an inhibition of spatial ability as measured in a number of tests including three of the traditional measures for field dependence. A similar inhibition of spatial ability could be observed in probands who had been subjected to cyclic estrogen treatment for many years. In contrast short-term cyclic estrogen treatment of Women with Turner's syndrome apparently could be related to activation of spatial ability to a level very much like that of their normal sisters. If confirmed these observations have a number of important practical and theoretical implications. They on the other hand also raised many pertinent problems.

The first problem was to find a model for describing the relation between duration of estrogen treatment and spatial ability. Evidently, a curvilinear model such as depicted in Figure 1 described the observations quite well.

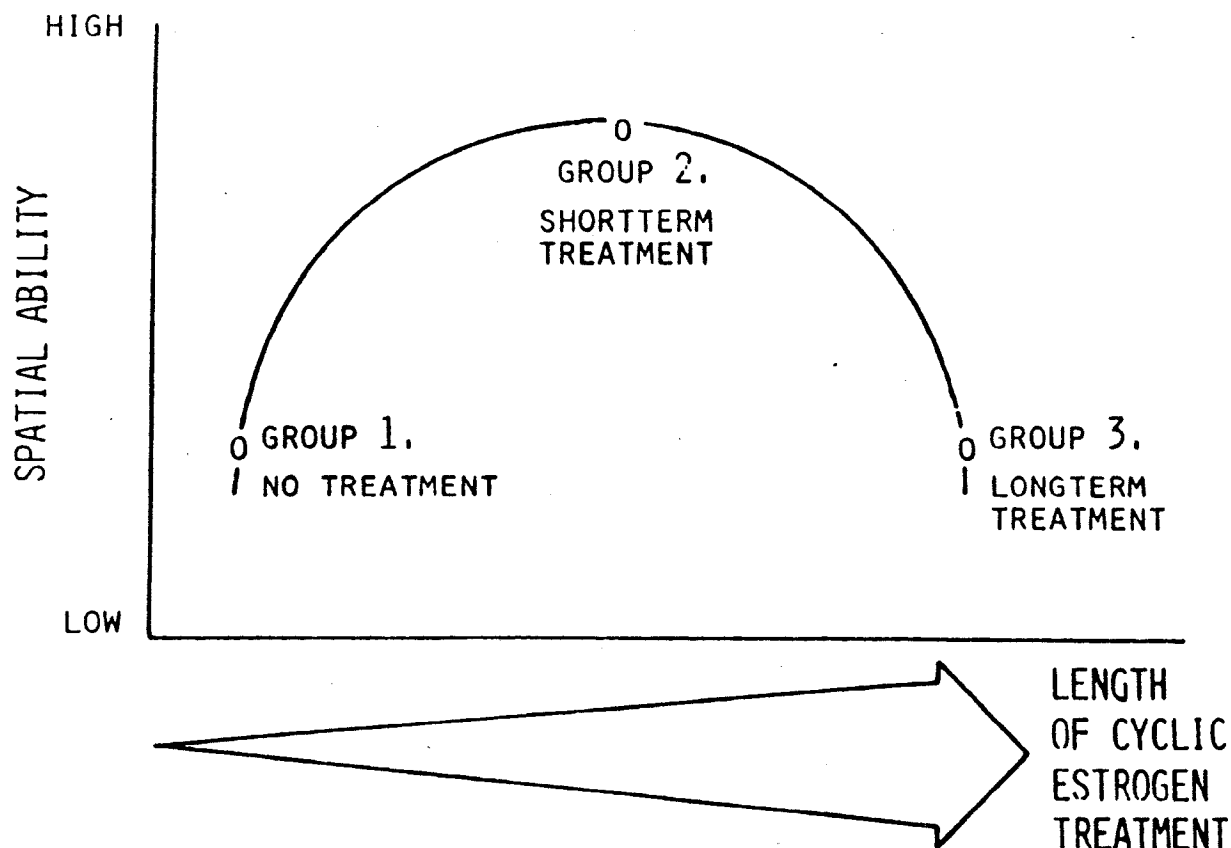


Fig. 1. A curvilinear model for the relationship between spatial ability and duration of cyclic estrogen treatment in women with Turner's syndrome.

The curvilinear model would be invalid if age at which treatment began, and not duration of treatment, was the important variable that explained our results. Thus a too early initiated cyclic estrogen treatment might damage the development of spatial ability in the probands while treatment commenced at a later age might facilitate spatial ability. However, the mean age at which cyclic estrogen treatment was begun was nearly identical in the short-term treatment group and in the long-term group: 17 years 9 months (SD 1 year) versus 17 years 7 months (SD 4 years 1 month) respectively. Pooled data from the two treatment groups were furthermore analysed in order to examine if probands commencing cyclic estrogen treatment before their eighteen year birthday performed differently from those initiating cyclic estrogen treatment at a later age. No difference between early and late commencement was found, and it was concluded that early or late onset of cyclic estrogen treatment was not an important variable in the present study. As fashion in drugs used and in dosage characteristic of one period may have differed considerably from another period, such a difference could perhaps explain the significant difference in spatial ability between groups. However, cyclic estrogen treatment was instigated in the two groups with an average temporal difference of about one year, making the differential treatment idea untenable. We therefore concluded that cyclic estrogen treatment influence the expression of spatial ability in women with Turner's syndrome, and further that duration of treatment is essential for the effect.

The next problem arose because the curvilinear model was not intended to just mirror a static description of the observations, but rather to be an implement for understanding the dynamic impact of estrogen treatment on the development of spatial ability in the probands. Taken as such the curvilinear model imply for example that the short-term treated probands profitted by the cyclic estrogen treatment by raising during therapy their initially low spatial ability score to a level indiscriminable from that of normal women in parallel with the forced maturation of the secondary sexual characteristics. The model further imply that the long-term treated probands followed this same favourable

developmental course which, however, was succeeded by a significant inhibition of spatial ability as a concomitant to prolongation of cyclic estrogen therapy. Even if this dynamic impact of estrogen on spatial ability had been observed rather than inferred there would still be no answer to important questions like: "Why do untreated probands perform so badly on spatial tests?", "How could estrogen influence the level of spatial ability?", and "How could long-term estrogen treatment inhibit spatial ability?".

Due to the very nature of this retrospective study and due to lack of comparable studies the two implications of the curvilinear model are still not tested, and the need for a replication is evident. We have, however, evidence from more independent sources, not only to support the idea of a curvilinear relationship between estrogen treatment and the expression of spatial ability, but also providing tentative answers to the above mentioned three questions. The following discussion of this evidence is based upon the acceptance of the following assumptions: (1) adequate adult neural functioning presupposes a pre-pubertal period of "normal" neural growth and structural differentiation, (2) spatial ability presupposes "normal" neural functioning (as damaging certain brain areas in the right hemisphere often leads to impaired spatial ability), and finally (3), that estrogen have qualitative different effect depending between other things upon duration of treatment.

The tentative answer to the first question of why untreated probands perform so badly on spatial tests was connected to the first assumption by suggesting that the women with Turner's syndrome in parallel with their delayed somatic development in general also suffer from an abnormal neural development of certain brain areas (for review, see 2). This abnormal development is for example manifested by the abnormal EEG's in a number of probands although it should be noted that their EEG's usually do not deviate grossly. Thus electroencephalographic examination of 39 at the 45 probands from which the present sample was drawn showed that while a completely normal EEG picture could be found in 38 per cent, another 38 per cent revealed borderline abnormal EEG and 23 per cent of the probands manifested a slightly abnormal EEG². Based upon the second assumption we now suggest

that the low spatial ability in untreated probands might reflect their developmental neural abnormalities although admittedly very little can presently be said about the specific connection. It is, however, interesting in this connection to note that Christensen and Nielsen²⁰ when applying Luria's neuropsychological method could observe a decreased function in Turner's women in the tertiary zone, postcentrally in the right hemisphere, and basally in the frontal part, but they did not find a general diffuse cerebral aberration. At this point the question of how estrogen could influence spatial performance was connected to the third assumption that estrogen may have not only quantitatively but also qualitatively different effects on the growing organism. Thus it has been shown that estrogen stimulates neural growth processes^{14,15} and, what is important in the present context, that neural growth and structural differentiation does not take place in the complete absence of estrogen¹⁶. Accordingly it seems reasonable to assume that low spatial ability in untreated probands reflects delayed neural development which to a certain degree is secondary to an abnormally low level of estrogen in the prepubertal maturational period. By the same token it becomes understandable that short-term cyclic estrogen therapy might stimulate neural growth of the central nervous areas underlying spatial performance to an extent that thus treated probands reached the usual female level of spatial ability. This interpretation is in line with the notion that hormones have a more or less irreversible impact during differentiation and maturation periods¹⁷. Obviously the next thing to do is to study a new group of probands before and after exogenous administration of estrogen, and such an investigation is planned.

The third question about how long-term estrogen treatment could depress spatial ability is not easily understandable in terms of the notion that estrogen may facilitate neural growth. Probably therefore our preliminary linear model broke down, with the result that our observations appeared paradoxical. However, with the increasing knowledge in the field of neuroendocrinology it has become clear that excessive administration of estrogen might have some detrimental effects on neural tissue, and this observation might help explain why the long-term treated probands

scored low in the spatial tests. Thus Brawer et al.¹⁸ demonstrated that treatment of adult rats with high doses of estrogen causes degeneration of hypothalamic tissue and Döhler and Hancke¹⁹ suggested that super-maximal estrogen concentrations become toxic to normal neural differentiation leading in functional terms to a neural stage that would be comparable to an original undifferentiated level.

Further support for this point of view was provided by Dawson¹⁰ who demonstrated that a low single dose of estrogen (one subcutaneous implant) did not suppress spatial performance in rats, while a double dose led 30 days later to a significant deterioration of maze learning. Obviously research on rats cannot be directly implemented on the human level, but the parallel between the high dose effects in the animals, and the depression of spatial ability in long-term treated probands is intriguing and might support the tentative hypothesis that low spatial ability in long-term treated probands reflected either degeneration of and/or functional disturbances in neural tissues related to spatial ability secondary to prolonged estrogen treatment. Finally a slight but not significantly higher than expected number of long-term estrogen treated women with Turner's syndrome seem prone to develop endometrial cancer² possibly reflecting also a peripheral somatic reaction to unphysiological high doses of estrogen.

Summarizing the attempt to explain the observed curvilinear relationship between duration of cyclic estrogen treatment and development of spatial ability the following has been proposed: due to abnormal low level of estrogen untreated probands exhibit delayed somatic and neural growth the latter responsible for low spatial ability; moderate exogenous administration of estrogen enhance somatic and neural growth the latter development resulting in improved spatial ability; longterm administration of estrogen might cause degeneration of neural tissue with resulting in low spatial ability. It should be noted, however, that this account of the possible impact of estrogen on spatial ability apply specifically to the present abnormal population in terms only of the inductive effects of sex hormones. Activational effects of estrogen although also important for understanding spatial performance are not considered in the present work.

If replicable the present study indicated that it is essential in future studies of spatial ability in women with Turner's syndrome to control for estrogen therapy. Also it seems not feasible to juxtapose genetic transmission of colorblindness with genetic transmission of spatial ability in Turner's syndrome as the former is definitely a recessive X-linked trait not manipulable by hormones. Furthermore the present observations speak against the popular notion that low spatial ability is the result of strict maternal sex-typic female rearing because sexually more advanced women obtained a higher spatial score than did the sexually less distinguished women.

Our findings may also have clinical implications. A common mistake is to assume that some traits, such as spatial ability, are unchangeable and irreparable because they are under the influence of genetic factors. Our findings show, however, that proper hormone treatment may enhance spatial ability, at least in women with Turner's syndrome. The low spatial ability of long-term treated probands suggests, on the other hand, that cyclic estrogen treatment should be given only for a relatively short period of time until the desired development of the secondary sexual characteristics is achieved, i.e. 1-2 years. Such a relatively short period of treatment would also be expected to eliminate the possible increased risk of endometrial cancer.

When judging the present investigation a number of quite serious methodological limitations must however be born in mind. Thus the number of probands in each group was small; although all treated probands received estrogen in most cases this treatment was supplemented by gestagen; treatment schedules and dosage levels varied among doctors, and it was not possible to verify if the probands in fact allways took the prescribed doses. Furthermore throughout the discussion the implicit assumption has been made that duration of cyclic estrogen treatment could somehow be related to level of plasma estrogen, although this assumption could not be tested. Our attempt to explain the relation between estrogen, neural functioning and spatial ability also model a causal relationship that was inferred rather than proved in the pseudo-experimental design. In the light of the methodological shortcomings it becomes even more surprising that a clear and definite patterning could be seen in the data.

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