

Regional Cerebral Glucose Metabolism in Turner Syndrome

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ABSTRACT: Regional cerebral glucose metabolism was examined in females with Turner syndrome, a sex chromosome abnormality. Previous studies have found a visual/spatial cognitive anomaly in these women but, to date, no abnormalities in brain structure or function have been associated with the condition. In the present study, decreases in regional metabolism were found in the occipital and parietal cortex. The involvement of the occipital cortex, although consistent with the observed cognitive anomalies, has not been suggested previously as an area dysfunction. Because the occipital cortex is a primary sensory cortex, the reduction of glucose metabolism in the parietal cortex may reflect a lack of innervation from the occipital cortex. Besides insight into the functional specialization of the brain, these findings are also consistent with previous reports on animals regarding the effects of estrogen in brain maturation.

RÉSUMÉ: Métabolisme cérébral régional du glucose dans le syndrome de Turner Nous avons examiné le métabolisme cérébral régional du glucose chez des femmes porteuses du syndrome de Turner, une anomalie des chromosomes sexuels. Des études antérieures ont montré une anomalie cognitive visuo-spatiale chez ces femmes, mais à date, aucune anomalie dans la structure ou la fonction cérébrale n'a été associée à cette condition. Dans la présente étude, nous avons observé des diminutions du métabolisme régional dans le cortex occipital et pariétal. L'atteinte du cortex occipital, bien que compatible avec les anomalies cognitives observées, n'a pas été suggérée précédemment comme étant une dysfonction régionale. Parce que le cortex occipital est un cortex sensoriel primaire, la diminution du métabolisme du glucose dans le cortex pariétal peut refléter un manque d'innervation à partir du cortex occipital. En plus de fournir des indices sur la spécialisation fonctionnelle du cerveau, ces observations sont également compatibles avec des observations antérieures sur les animaux faisant état des effets des estrogènes dans la maturation du cerveau.

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In 1938, Turner reported a symptom triad of sexual infantilism, webbing of the skin of the neck and abnormal angle of the elbow (cubitus valgus) in seven female patients.¹ Turner syndrome was subsequently found to be associated with an absence or an abnormality in the second sex chromosome.² Shaffer³ reported that in persons with Turner syndrome verbal skills were relatively better than visual spatial abilities as measured by factor scores derived from the subtests of the Wechsler Adult Intelligence Scale (WAIS). He suggested that this cognitive disturbance in Turner syndrome women was caused by an organic defect arising from the sex chromosome abnormality. Further studies of cognitive abilities in these women have yielded different inferences regarding the site of the organic deficit. Alexander et al.⁴ reported defective figure drawing and later Money⁵ suggested that these cognitive anomalies may reflect right parietal lobe dysfunction. Kolb and Heaton⁶ and Silvert et al.⁷ have suggested generalized right hemisphere dysfunction based again on the pattern of cognitive anomalies. More recently, McGlone⁸ concluded that "a unitary explanation in terms of

focal CNS dysfunction or atypical speech representation cannot account for the pattern of neuropsychological deficits seen in Turner syndrome" (p. 375).

No consistent structural abnormality in the brain has been identified in neuropathological studies of Turner syndrome.⁹ Early evoked potential and electroencephalogram studies in Turner syndrome patients have identified no lateralizing or localizing signs.¹⁰ However, more recently changes in frequency, amplitude or amount of alpha, theta, delta and beta waves more pronounced in the left hemisphere have been reported.¹¹ In the current study, five females with Turner syndrome were studied by means of positron emission tomography (PET) using the ¹⁸F-fluorodeoxyglucose (FDG) tracer analogue for glucose metabolism¹² and compared to six age-matched female controls. All subjects were psychologically assessed prior to the PET/FDG scan. The purpose of the study was to determine if a metabolic substrate could be identified that may be related to the observed cognitive anomalies.

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METHODS

Subjects

The five subjects with Turner syndrome were physically examined and karyotyped. All five had typical physical characteristics associated with Turner syndrome. Three were karyotyped as 45X, one as 45X/46XX and one as 46X, i(Xq). Two of these five persons were on oestrogen replacement therapy (Premarin 0.625 mg daily). Their mean age was 27.8 years (SD = 5.45, range 19-34) with 12.8 years of education (SD = 1.10, range 12-14). Four of the subjects were employed doing clerical/technical tasks while one had recently graduated from high school and was seeking employment. Four of the subjects were right handed. The six normal controls were drawn from a sample of female identical twins such that only one twin of each pair was selected and their ages were comparable (mean age = 28.7, SD = 3.88, range 24-34). The member of each pair was selected randomly. The twin data was collected as part of another study where, besides PET scans, similar neuropsychological tests were administered. The mean education level of this group was significantly higher than the Turner subjects (mean = 15.8 years, SD = 2.5, range 12-19; $t = 2.52$, $df = 9$, $p \leq 0.05$). At the time of assessment three of the controls were employed, two were students and one was seeking employment. All normal controls were right handed. Informed consent was obtained from all subjects and the study was approved by the UBC Human Research Committee.

Neuropsychological Battery

The psychological battery consisted of the Wechsler Adult Intelligence Scale, the Benton Visual Retention Test, the Finger Tapping Test, Strength of Grip, Word Fluency (FAS), Halstead Category (shortened form) the Tactual Performance Test (6-

block version) and a Dichotic Listening Test (triads of word pairs). These tests were administered by a trained psychometrist who was unaware of previous research findings in Turner syndrome. The order of testing was random.

PET Scan Procedures

All PET scans were performed with the UBC/TRIUMF PET VI scanner (average in-plane resolution = 9.2 mm FWHM).¹² Two transmission scans (Ge-68 ring source) were done separated 7 mm in the axial direction. Head placement was verified by applying a reconstruction algorithm to the transmission data that produce a medial sagittal view of the density distribution in the skull and brain. Head position was maintained throughout the transmission and subsequent emission scans by means of a thermally fitted plastic mask. Thirty-five minutes after the injection of FDG (3-5 mCi), two 15 minute emission scans were performed in positions corresponding to the transmission scans. Serially timed venous blood samples, "arterialized" by heating the arm, were drawn starting with the FDG injection and continuing until the end of the second emission scan. ¹⁸F-radioactivity was counted in a scintillation well counter while plasma glucose was measured before the FDG injection and at intervals during the scan. Regional metabolic rates were calculated using Brooks' form of the original Sokoloff equation.^{14,15} A value of 0.418 was used for the "lumped constant" with literature values for the four rate constants for grey matter.¹¹

All subjects were scanned in the morning after a breakfast of toast with no butter and tea with no milk or sugar to control partially for potential variations in the lumped constant resulting from different glucose levels.¹⁶ During the entire scanning procedure, an attendant was present and periodically ensured the subject was awake and comfortable. During the tracer uptake period, the subject's eyes were covered and the room darkened

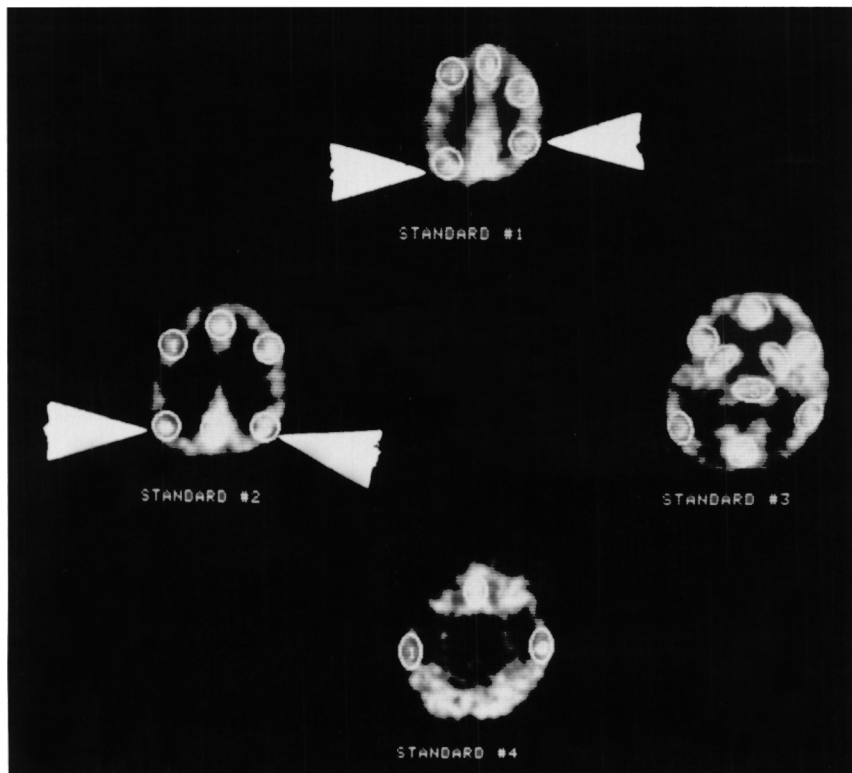


Figure 1 — The four slices and their respective regions of interest with the four regions with significant reductions in metabolism indicated by arrows.

but the ears were not occluded.

The scanning protocol yielded fourteen axial slices with a slice centre to centre separation of 7 mm. For each subject, four of these 14 slices were selected corresponding to the following levels: 1) cortical mantle (Slice I); 2) the paired lateral ventricles at the level of the genu of the corpus callosum (Slice II); 3) the body of the caudate and putamen (Slice III); and 4) orbital frontal cortex and the lateral temporal lobe (Slice IV). On each of these slices, regions of interest of fixed area (1.7 cm²) were placed to correspond with gross neuroanatomical features (e.g. frontal lobe, occipital lobe) and to maximize the measured metabolic value for that region.¹⁷ These procedures resulted in 24 regions of interest. The four slices with their respective regions of interest are given in Figure 1. The derived metabolic rates for each region were compared between the groups by means of t-tests.

RESULTS

The group means and standard deviations for the WAIS and the neuropsychological battery are presented in Table 1. The Full Scale Intelligence Quotient (FIQ) for the Turner group was significantly lower than the estimate for the controls, with the Verbal estimate (VIQ) being significantly lower and the Performance estimate (PIQ) approaching significance. The mean FIQ for the controls was at 58 %ile of the distribution of general intelligence or the normal range whereas for the Turner group, the mean FIQ was at 25 %ile or at the upper end of the dull/normal range. Within each group, the VIQ and PIQ estimates were almost identical. For the neuropsychological battery on five of the fourteen variables, the Turner group's performance was significantly lower than the control group. These variables were the Benton Visual Retention Test, the Halstead Category Test, the Word Fluency Test and the right and left dynamometer measures.

The metabolic rates of the two groups for each of the twenty-four regions of interest are presented in Table 2. Four of the resulting t-values were significant. The regions with significant reductions in glucose metabolism were the left and right parietal cortex on Slice 1, the left parietal cortex on Slice 3 and the occipital cortex on Slice 3. These regions are marked with arrows on Figure 1. To ensure that the found differences were not a function of a general decrease in glucose metabolism that was slightly more pronounced in the posterior region, an occipital/parietal to frontal ratio was calculated for each subject. These ratios are plotted for each subject in Figure 2. From this figure, it is clear that the parietal to frontal ratio was higher in every control than any Turner subject. Oestrogen replacement therapy did not affect this differentiation. This clear separation of the two groups indicates that the reported significant differences in absolute metabolic rate truly reflect a selective regional decrease in metabolism.

DISCUSSION AND CONCLUSIONS

Before reviewing the metabolic findings and their possible relationships to functional specialization and brain maturation, the genetic, demographic and psychological characteristics of this sample should be compared to previous studies of Turner syndrome. From a genetic perspective, three of the subjects were missing the second sex chromosome entirely, one had a

mosaic karyotype of 45X/46XX and one had 46X,i(Xq) isochromosome. Although it has been hypothesized that variations in the karyotype may cause consistent variations in physical and psychological features, no patterns have been discerned. In this

Table 1: Group Means for the WAIS and Neuropsychological Tests

	Normal X(SD)	Turner's X(SD)	t-value
WAIS: VIQ	103.5 (4.9)	89.4 (7.9)	3.63 ^b
PIQ	103.7 (8.4)	91.0 (11.7)	2.09
FIQ	103.2 (5.0)	89.0 (7.7)	3.67 ^b
Benton Visual Retention Test (Errors)	2.2 (1.7)	5.2 (1.9)	2.76 ^a
Category (Errors)	14.8 (6.5)	30.4 (13.5)	2.50 ^a
Word Fluency (Total)	40.2 (9.1)	27.8 (5.7)	2.62 ^a
Finger Tapping			
Right	46.6 (4.6)	42.9 (7.5)	1.00
Left	42.9 (1.5)	41.2 (6.7)	0.61
Dynamometer			
Right	36.0 (6.0)	18.3 (5.3)	5.11 ^c
Left	32.3 (4.7)	15.2 (5.3)	5.68 ^c
Dichotic Listening			
Right	24.0 (8.2)	16.0 (9.6)	1.42
Left	25.4 (12.0)	22.4 (9.4)	0.44
Total (R + L)	49.4 (10.8)	38.4 (11.8)	1.54
Difference (R - L)	-1.4 (17.4)	-6.4 (14.9)	0.49
Tactual Performance Test			
Total time (min)	4.0 (1.4)	6.6 (4.1)	1.39
Memory	5.2 (0.8)	4.2 (1.5)	1.40
Location	4.2 (1.0)	2.8 (1.6)	1.71

a: p ≤ 0.05 b: p ≤ 0.01 c: p ≤ 0.001

Table 2: Rates and Standard Deviations of Regional Cerebral Glucose Metabolism

Slice	Region	Normal	Turner's	t-value
I	Anterior Frontal	9.3 (1.0)	8.8 (1.0)	0.72
	Left Frontal	8.8 (0.9)	8.4 (1.0)	0.63
	Right Frontal	9.6 (1.0)	8.6 (1.1)	1.65
	Superior Parietal	10.4 (1.7)	9.2 (1.8)	1.18
	Left Parietal	9.8 (1.1)	8.0 (1.5)	2.31 ^a
	Right Parietal	9.7 (1.0)	7.8 (1.4)	2.66 ^a
II	Anterior Frontal	9.3 (1.0)	8.8 (1.1)	0.91
	Left Frontal	9.1 (1.0)	8.2 (1.3)	1.42
	Right Frontal	9.5 (0.8)	8.9 (1.2)	0.94
	Superior Parietal	11.0 (1.0)	10.0 (1.5)	1.31
	Left Parietal	9.3 (1.2)	8.1 (0.9)	1.89
	Right Parietal	9.5 (1.0)	8.3 (1.1)	1.92
III	Anterior Frontal	9.2 (1.1)	8.6 (1.0)	0.96
	Left Frontal	8.9 (0.7)	8.3 (1.0)	1.10
	Right Frontal	9.5 (1.0)	9.0 (0.9)	0.86
	Left Basal Ganglia	9.1 (0.9)	8.2 (0.7)	1.93
	Right Basal Ganglia	9.2 (0.8)	8.1 (0.8)	2.16
	Thalamus	8.2 (1.2)	7.9 (0.7)	0.48
	Occipital	10.1 (0.9)	8.8 (0.9)	2.28 ^a
	Left Parietal	8.6 (0.8)	7.3 (1.0)	2.34 ^a
Right Parietal	8.7 (0.8)	7.7 (1.0)	1.92	
IV	Anterior Frontal	8.4 (1.1)	8.2 (1.1)	0.34
	Left Temporal	7.7 (1.0)	6.8 (0.6)	1.82
	Right Temporal	8.1 (0.7)	7.4 (1.0)	1.3

a: p ≤ 0.05

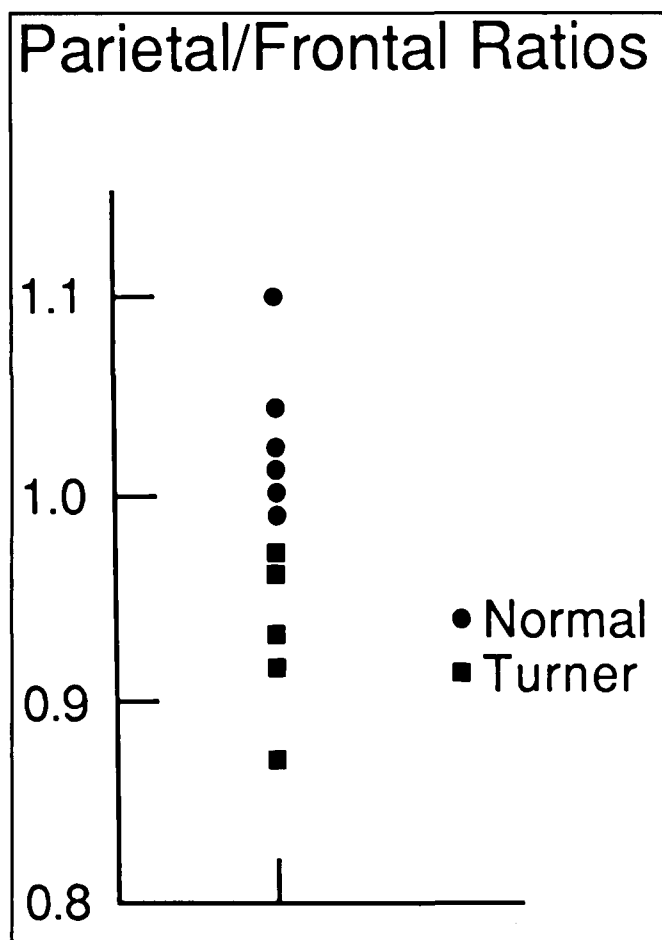


Figure 2 — The distribution of parietaloccipital to frontal ratios by group.

regard, there is considerable variation in the phenotype expressed by the 45X genotype. It should also be noted that approximately 99 percent of conceptions with Turner syndrome spontaneously abort.¹⁸ Therefore, the subjects in this study, or any study of Turner syndrome, represent a pre-selected or survivor sample and hence, the true effects of a karyotype missing the second sex chromosome on the phenotype are only partially represented.

With respect to previous psychological studies of Turner syndrome, the sample in the current study was on average considerably older ($X = 27.8$ years) than samples in previous studies. For example, the mean age was 15.9 years in the Shaffer³ study, 15.3 years in the McGlone⁸ study and 12.1 years in the Bender et al.¹⁷ study while the age range was 12-22 years in the Silbert et al.⁷ study. As this sample was older than previous samples, there may also be a selection bias operating in that four of five subjects were employed at the time of the study and all five had completed high school. However, the mean FIQ estimate is similar to those reported previously. Unlike previous studies, we did not find a large VIQ/PIQ discrepancy, rather the two estimates were almost identical. When considered individually, two subjects had VIQ and PIQ estimates that were almost identical (± 4 pts), two had evidence of a verbal superiority (7 and 13 pts) and one had a definite superiority on the performance subtests (22 pts). Whether the failure to find the expected verbal/perfor-

mance discrepancy is a function of the small sample size, a selection bias, age related differences in the WISC/WAIS standardization procedures or some differential aging process in Turner syndrome compared to normals could not be determined.

The neuropsychological findings are also not entirely consistent with the previous studies of younger Turner subjects. First, in the motor domain, the subjects in this study are considerably weaker in terms of grip strength in comparison to normal controls. Earlier studies have not found such a large difference, probably because the subjects were still physically maturing. However, on the Finger Tapping Test, a test of motor speed, the performance of the two groups was almost equivalent. In addition, no differences were found in psychomotor integration as measured by the Tactual Performance Test. One Turner subject had extreme difficulty with this test and if this subject is removed from the analysis, the means are almost identical. Although the results of the Dichotic Listening Test are not significant, the observed differences are consistent with Netley and Rovet,²⁰ finding that Turner subjects are less likely to show a right ear advantage. However, unlike Netley and Rovet, we did not do audiometric screening of our subjects and hence, our findings may be suspect as hearing problems are not uncommon in Turner syndrome. The three neuropsychological variables where significant differences were found are of particular interest. Two of the tests, the Halstead Category and the Benton Visual Retention Test, require processing of visual stimuli. Although the greater number of errors on the Benton may be related to the poorer drawing skills associated with Turner syndrome, such a hypothesis cannot explain the poorer performance on the Halstead Category Test, rather the deficit must be related to visual perception, integration or concept formation. The poorer performance on the Word Fluency Test has not been reported previously although McGlone⁸ did administer a version of this test to her younger sample. The psychological findings of this study suggest that cognitive anomalies do persist into adulthood in Turner syndrome but the nature of the anomaly may change.

The cardinal finding of the current study is the reduction in regional cerebral glucose metabolism in the occipital and parietal cortex. Moreover, given the small sample size and the known magnitude of individual differences in absolute glucose metabolism,²¹ the observed reductions are quite marked. Although involvement of the parietal cortex has been suggested as the reason for the observed cognitive discrepancies, a disturbance of the primary visual cortex has never been suggested as a potential area of dysfunction in Turner syndrome. One reason for not hypothesizing the involvement of the occipital cortex is that subjects with Turner syndrome exhibit very few of the deficits traditionally associated with occipital lobe lesions such as hemianopsia, scotoma or pronounced visual distortions of shape, distance, color or size.²² Rather, the observed impairment is more consistent with disturbance of parietal lobe function. Perhaps the only deficit that is consistent with an occipital lobe lesion is the poor drawing abilities. However, the subtlety of the effect is illustrated by the fact that for most Turner subjects, reading is one of their better acquired skills.

Because glucose metabolism measures brain activation rather than structure, the question arises whether the reduction in parietal metabolism is a function of a lack of parietal innervation due to the reduced activity of the occipital cortex or whether

there are truly parietal lobe abnormalities. Specifically, if the input to parietal cortex via primary and secondary occipital projections is reduced due to occipital lobe inactivity, it is possible that parietal lobe metabolism accordingly is reduced. Therefore, this reduction is secondary to the occipital lobe dysfunction. Alternatively, the reductions in regional glucose metabolism may be caused by a disruption of neuronal proliferation and migration during fetal life and early infancy. This disruption of neuronal proliferation and migration may be a result of the disturbed hormonal environment of persons with Turner syndrome. It has previously been shown that in the rat, neuronal migration and assembly may be modulated by circulating sex hormones.^{23, 24, 25} Moreover, estrogens enhance cortical maturation and myelogenesis in the rat and at the time of peak estradiol levels, there is an associated intense sprouting of neurites and myelination of axons. Whilst two of the five persons with Turner's syndrome were on oestrogen replacement therapy, this was started late in life, long after the expected period of cortical maturation. Hence, the ovarian dysgenesis with lack of estrogen secretion associated with Turner syndrome could conceivably result in disturbed myelogenesis. In this regard, castration of female rats at birth has been shown to alter the normal predominance of the posterior left hemisphere cortex in comparison to the right. One of the areas particularly affected is the visual integrating centre.²⁶ It is possible that, similar to the rat, functional castration has significant influence on brain development particularly affecting the occipital and parietal cortex and thereby resulting in reductions of regional glucose metabolism. Therefore, the finding of selective regions of reduced glucose metabolism in subjects with Turner syndrome may provide further evidence that female sex hormones have significant effects on brain maturation.

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