

Reduced brain perfusion and neurocranial shape abnormalities of the temporal regions in patients with Klinefelter syndrome

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Abstract

OBJECTIVES: In patients with Klinefelter syndrome dissocial behaviour, learning difficulties and low intelligence are common. Thus, the aim of our study was to perform brain perfusion studies and cranial cephalometry in 27 cases of Klinefelter syndrome and compare the results with those in a group of 26 healthy subjects.

METHODS: Single photon emission tomography (SPECT) was performed after injection of 20 mCi ^{99m}Tc-HMPAO and the data from transaxial slices were analyzed for 46 regions of interest in the cerebellar, thalamic, ventricular and parietal planes. Right/ left ratios were calculated and differences above 10 per cent were considered abnormal. Skull radiographs in frontal and lateral view were taken and measurements of the cerebral part were made.

RESULTS: SPECT imaging in 27 Klinefelter patients revealed 82 hypoperfusion foci, most frequently in temporal regions, less frequently in temporoparietal and frontal regions, whereas only 11 hypoperfusion foci in 6 of the 26 control subjects were found. Skull radiography revealed the following abnormalities: flattening of the temporal regions, reduced width of the vault, shortening of the anterior cranial fossa and definitely reduced angle of the cranial base; all these anomalies differed significantly from those in the skulls of the control subjects.

CONCLUSIONS: The high coincidence of the location in the temporal regions of brain perfusion defects and the neurocranial shape anomalies indicate that an extra X chromosome in Klinefelter patients has detrimental effects on the temporal lobe development and function.

Introduction

Klinefelter's syndrome is the most frequent form of male hypogonadism, it occurs in 1 of 1000 live-born males. Clinical manifestations of Klinefelter syndrome involve hypogonadism of varying degree, atrophic testes, azoospermia,

diminished facial and body hair and frequently gynaecomastia. In childhood there are usually no clinical signs of the disease. Puberty is delayed, later in life diminished libido and, invariably, infertility are evident. Chromosome studies reveal

a 47, XXY karyotype. Dissocial behaviour is common, the patients demonstrate aggravated responses to faint stimuli. In childhood the patients show deficits in language processing and learning difficulties, significant underachievement and frequent grade failure (4, 6, 14, 17). Later in life they have personality problems and difficulties in psychosocial integration. Geschwind et al (5) studied the neurobehavioral phenotype of Klinefelter patients; based on results of their studies they suggested that altered left hemisphere dysfunction is at the core of the patients language problems. In studies of Boone et al (3) based on observations of 35 cases, the Klinefelter patients scored below controls in language skills and verbal processing speed. Reiss et al (13) paid attention to reduced performance on tests of reading skill, retrieval and verbal IQ in patients with Klinefelter syndrome.

Because of frequent behavior problems, learning difficulties and lowered IQ in Klinefelter patients with 47, XXY karyotype the aim of our study was to perform brain perfusion and skull radiography to explore whether brain structure and function are altered. We have found an amazingly high incidence of abnormalities in brain perfusion, and neurocranial shape in the temporal regions of the brain. A detailed description of these alterations forms the basis of this report.

Material and methods

Study population. Our study comprised 27 patients with Klinefelter syndrome, aged 17 to 47, with 47, XXY karyotype. The patients sought medical attention because of deficient sexual development, gynaecomastia or infertility. On physical examination the patients were tall, their stature was greater than the height of their fathers or brothers. The lower extremities were elongated in comparison to the trunk. Twelve patients had gynaecomastia. The body hair was markedly reduced, the beard growth was scanty and the pubic hair was of a female escutcheon. The size of the external genitals varied from hypoplastic to normal but the testes in all patients were invariably small and firm. Serum FSH were definitely elevated, serum LH moderately increased, and serum testosterone concentrations were in the low-normal range or reduced. On neurological examination essential tremor was diagnosed in 2 patients but no focal changes were found. In 7 patients computerized tomography of the brain was performed;

on 3 patients the lateral ventricles were slightly or moderately enlarged, but no focal lesions were detected.

Electroencephalography was carried out in all patients. In 20 cases abnormalities were found, in both temporal regions theta waves, usually 5 to 7 c/s, were recorded and in 12 cases sharp waves in these regions were also observed. These EEG abnormalities appeared more frequently on the left side.

Psychological tests in our patients disclosed a lowered IQ, ranging from sluggishness to mental deficiency of a slight degree. Deficient mental development was manifested not only in psychological tests but also in difficulties to obtain suitable education and professional status that was definitely inferior in comparison to their healthy siblings.

Brain perfusion

Single photon emission tomography (SPECT) was performed after intravenous (i.v.) injection of 740 MBq (20mCi) ^{99m}Tc -HMPAO (hexamethyl-propyleneamine oxime). Radiotracer was administered to patients according to manufacturer's instruction and imaging was begun 5–40 min later in a quiet and dimly lit room. SPECT images were obtained using a rotating gamma-camera equipped with a low-energy high-resolution collimator (Siemens, Diacam) connected to an ICON computer for three-dimensional reconstruction. Data were collected from 90 angular increments over 360 degrees in 64x64 matrices with an acquisition time of 20s per view. The camera was set for elliptical rotation, with a 15% energy discrimination window centered at 140 keV. Orthogonal transverse, sagittal and coronal slices were generated by filtered back projection using a Butterworth filter (cut off frequency 0.45, order 7). The reconstructed transaxial image was 8 mm thick per slice. Semiquantitative analysis of the cortical ^{99m}Tc -HMPAO uptake was performed by means of the circumference profile method. Twelve regions of interest (ROIs) were drawn bilaterally in the parietal, ventricular and thalamic planes and 10 ROIs in cerebellar areas on transverse slices with references to an anatomical map. The counts per pixel in each ROI were calculated and the ratios of the counts per pixel in the cerebral cortical ROIs to those in the cerebellar ROIs were obtained. The relative regional cerebral blood flow (rCBF) was expressed as the ratio of regional to cerebellar activity. Interhemispheric side-to-side asymmetry indices for

Figure 1. A scheme of the measurements taken from skull radiographs.

Fig 1. **A** – shows cranial base angle (n-tu-b) of 133° in a normal subject.

Fig 1. **B** – displays a decreased angle 128° in a 29-year-old patient with Klinefelter syndrome

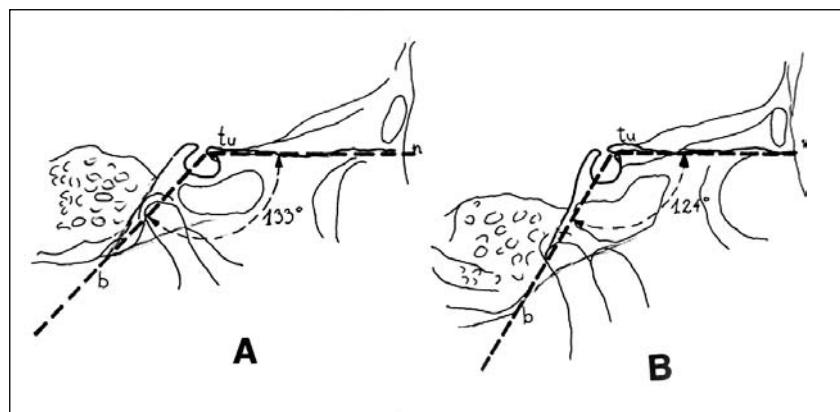


Table 1: Distribution of hypoperfusion foci in Klinefelter patients.

Section / lobe	Right hemisphere				Left hemisphere			
	Frontal	Temporal	Temp/Parietal	Occipital	Frontal	Temporal	Temp/Parietal	Occipital
Cerebellar	-	8**	-	-	-	8**	-	-
Thalamic	3	5*	-	1	7**	11***	-	-
Ventricular	2	-	1	3	5*	-	8**	1
Parietal	1	-	-	1	2	-	13***	2
Sum	6	13	1	5	14	19	21	3
Total	25***				57***			

Distribution of hypoperfusion foci in control subjects

Section / lobe	Right hemisphere				Left hemisphere			
	Frontal	Temporal	Temp/Parietal	Occipital	Frontal	Temporal	Temp/Parietal	Occipital
CCerebellar	-	-	-	-	-	-	-	-
Thalamic	2	-	-	-	-	1	1	-
Ventricular	2	-	1	1	-	1	-	-
Parietal	1	-	1	-	-	-	-	-
Sum	5	-	2	1	-	2	1	-
Total	8				3			

Statistical significance * p < 0,05 ** p < 0,01 *** p < 0,001

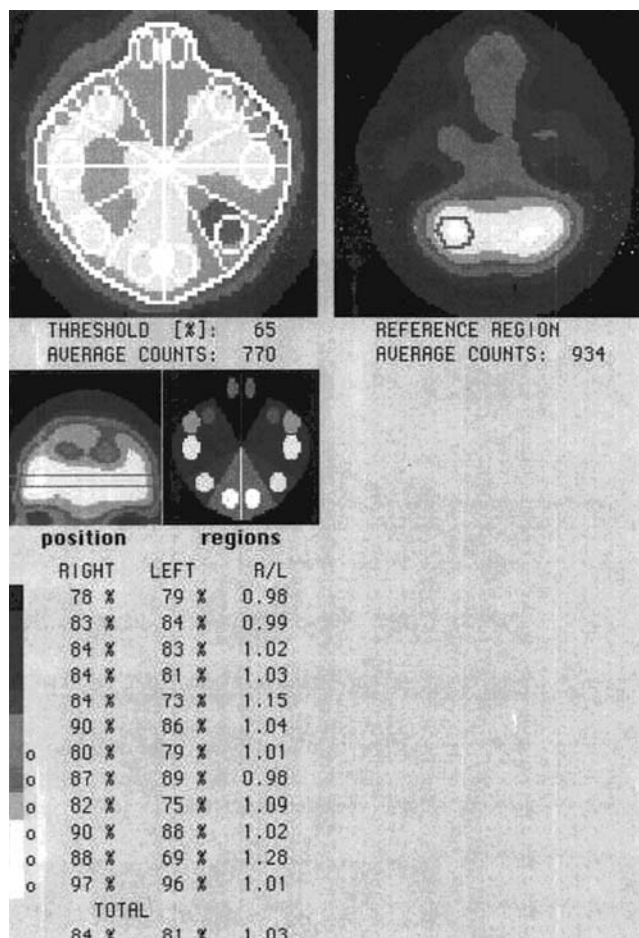


Figure 2. SPECT imaging of the brain of a 27-year-old Klinefelter patient displays a diminished regional blood flow in the temporo-occipital lobe.

mirrored sets of predefined ROIs were calculated. Only regional asymmetries surpassing 10% were considered as abnormal. For each right or left cortical region the radioactivity count densities of corresponding ROIs were averaged. Statistical analysis : Quantitative parameters were expressed as mean ± SD. Differences between controls and Klinefelter patients were analyzed using the test of significance for two fractions; for this purpose the U-test was used. The same statistics were applied for comparison of asymmetry between brain left and right hemispheres in KS patients. A value of P<0.05 was considered statistically significant.

Skull radiography

In all patients radiographs of the skull in frontal and lateral view were taken and cephalometry made. On frontal films the maximum width of the cranial vault was measured. On lateral films the length of the anterior cranial fossa (the distance between nasion and tubercle of the sella, n-tu) and the angle of the cranial base were measured. The cranial base angle is formed by the intersection of two lines, the first running through the base of the nose (n) and tubercle of the sella (tu) and the second line running through this tubercle and the anterior border of the foramen magnum (b) as shown in Fig. 1. These measurements were selected as our earlier observations have indicated that these parameters are abnormal in patients with sex chromosome aberrations (10, 15). Results of these cephalometric studies were compared with those on skull films of 50 male subjects in the same age range. All radiographs were taken from the same distance of 36 in (91.4 cm) from the tube to the table and 38 in (97 cm) distance from the tube to the film; this caused a magnification of the measured

Table 2: Skull radiography anomalies in Klinefelter syndrome

Anomaly	Klinefelter patients mean SD	Control subjects mean SD	Statistical significance
Width of cranial vault	17.7 ± 0.42 cm	18.1 ± 0.46 cm	P < 0.01
Anterior cranial fossa length (n-tu)	6.3 ± 0.22 cm	6.9 ± 0.23 cm	P < 0.001
Cranial base angle (n-tu-b)	128° ± 1.9°	133° ± 0.99°	P < 0.001

dimensions in comparison to their anatomical size. However, no corrections were made in the patients and control subjects results.

Statistical evaluation included unpaired t test with Welch correction, assumption test and Fischer's exact test. A P value of 0.05 or less was considered statistically significant.

The study was approved by the University Ethics Committee and the patients consented to these examinations.

Results

Brain perfusion

SPECT studies revealed hypoperfusion foci in all patients with KS, this means that no patient showed a homogenous marker distribution within the regions of the entire cerebral cortex. The perfusion asymmetry right : left within cortex regions was between 11 to 28 per cent. In 11 patients one focus of hypoperfusion was observed whereas in 16 patients two or three foci were found. Some foci of hypoperfusion included two, three or four ROIs. In the right hemisphere 13 hypoperfusion foci were found in the temporal lobes, 6 foci in frontal and 5 foci in occipital lobes. In the left hemisphere hypoperfusion areas were twice as common as on the right side and located in the frontal (14 foci), temporal (19 foci) and temporoparietal regions (21 foci). Reduced perfusion defects were more common in the left hemisphere in which 57 foci (ROIs) were detected whereas 25 foci were present in the right hemisphere. The distribution and location of hypoperfusion areas and their statistical significance in Klinefelter's patients is presented in *Table 1*. *Figure 2* illustrates a typical SPECT image of a patient with KS.

In the control group we have found 11 hypoperfusion foci in 6 of the 26 subjects. There were 5 hypoperfusion foci in the right frontal lobe, two foci in the left temporal lobe, three foci in the temporoparietal and one focus in the occipital lobe.

The difference between controls and patients was statistically significant ($p < 0.01$).

Skull radiographs

In skull radiography in frontal view the most conspicuous finding in 15 patients was an abnormal shape of the cranial vault, which revealed a bilateral or unilateral flattening of the temporal regions. In these cases the maximum width of the skull was located higher than normal, in the parietal regions instead of the temporal regions. In all control subjects the contour of the temporal regions was convex. Configuration of skull radiograph typical of Klinefelter patients and of

a control case is shown in *Fig. 3*. The maximum width of the cranial vault, mean and standard deviation, in Klinefelter patients and control subjects amounted to 17.7 ± 0.42 cm and 18.1 ± 0.36 cm respectively, the differences were statistically significant with $p < 0.01$.

Lateral radiographs of the patients skull displayed 2 significant abnormalities : a definite shortening of the anterior cranial fossa (the distance between nasion and tubercle of the sella) and an abnormal angle of the base. The length of the anterior cranial fossa in Klinefelter patients measured 6.3 ± 0.22 cm with a range from 5.8 to 6.9 cm, whereas in control subjects it was 6.9 ± 0.23 cm, ranging from 6.6 to 7.5 cm.

The second anomaly in the Klinefelter patients was a decreased angle of the cranial base. This angle in Klinefelter patients averaged $128^\circ \pm 1.9^\circ$ ranging from 124° to 132° whereas in control subjects it was 133° ranging within very narrow limits of one degree only. The differences between Klinefelter patients and control subjects were statistically highly significant with $p < 0.0001$. (*Table 2*)

Discussion

Our studies using SPECT brain imaging in Klinefelter patients demonstrated a very high incidence of hypoperfusion foci of temporal regions. To our knowledge this is the first report describing brain perfusion defects in a large group of Klinefelter patients. SPECT studies are frequently performed and hypoperfusion foci observed in patients with cerebrovascular disease, acute stroke, dementia and other degenerative diseases as well as in patients after head injury. However, in our group of Klinefelter patients no one had head trauma or suffered from cerebrovascular disease or dementia, diseases that could be responsible for hypoperfusion of temporal regions. The appearance of hypoperfusion of temporal regions in young adulthood Klinefelter patients indicates rather an inborn defect of brain development.

Itti et al (9) provided evidence of anomalous cerebral laterality in adult patients with Klinefelter syndrome. Patwardhan et al (11) measured regional brain volumes in patients with Klinefelter syndrome and detected a significant reduction of left temporal gray matter volumes compared with control subjects. Warwick et al observed a significant decrease in whole brain volume and enlarged ventricles. Recently, Shen et al (16) have studied brain morphometry in 34 Klinefelter patients using a precise automatic whole brain method and found a set of atrophy of left insula, superior temporal gyri, middle-inferior temporal gyri and occipito-temporal gyri that is in brain areas involved in verbal and

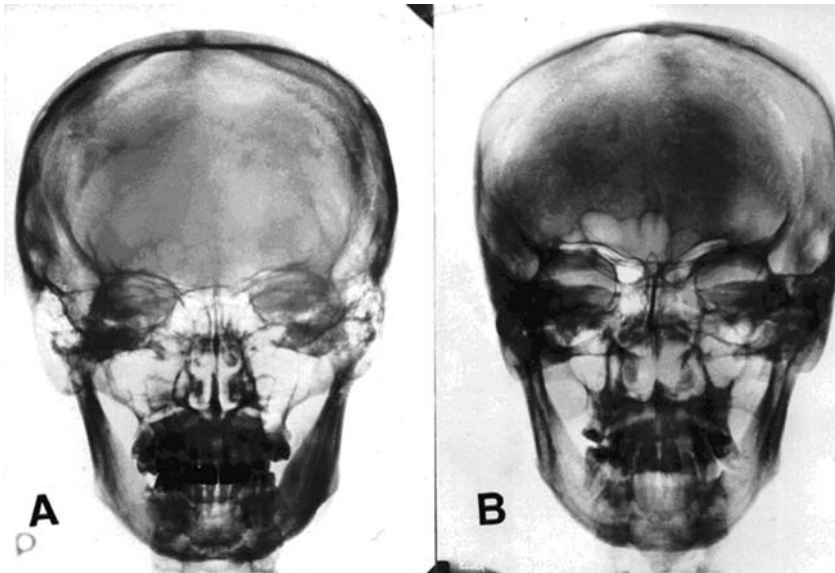


Figure 3. Frontal radiographs of the skull of a normal subject (A) and a 32-year-old Klinefelter patient (B) illustrate the difference in the shape of the calvaria. A marked flattening of the temporal bone is seen in the Klinefelter patient in comparison to the control.

language processing. These results correlate favorably with our SPECT findings of multiple hypoperfusion foci in the temporal lobes, particularly on the left side, and cephalometry indicating reduced volume of temporal regions. It is of interest that EEG abnormalities in our Klinefelter patients were localized in temporal lobes, that is, in regions in which perfusion defects were more prominent. In patients with X chromosome anomalies EEG abnormalities and seizures have been described by Grosso et al (7).

Skull radiographs and cephalometry in our Klinefelter patients confirmed our early observations that flattening of the temporal regions, reduction of the skull width, shortening of the temporal cranial fossa and reduced angle of the cranial base are frequently found. Babic et al (1, 2) and Ingerslev and Kreiborg (8) performed detailed cephalometric studies in Klinefelter patients and found a definite reduction of the cranial base angle, shortening of the anterior cranial fossa and some craniophacial anomalies. Ratcliffe et al (12) reported on diminished head circumference in their group of Klinefelter males. The described skull anomalies seem to be specific of Klinefelter's syndrome as they are not seen in other endocrine diseases (10, 17). It is well known that during the growth period, cranial bone shape, and size strictly adapt themselves to brain growth and development. Thus, flattening of the temporal regions and reduced skull width as well as shortening of anterior cranial fossa indicate that parts of Klinefelter patients brain, particularly the frontal and temporal regions, are of reduced volume. The base of the skull develops from cartilage and in fetal life the cranial base angle gradually decreases. In postnatal life it is one of the most stable parts of the skull, it does not change from childhood to adult life, it remains the same in both sexes and is independent of hormonal disturbances. This indicates that pathologic changes in cranial base development might have occurred in the prenatal period.

Conclusions

From results of our study we conclude that a high coincidence of brain perfusion defects in the temporal regions and neurocranial shape and size anomalies indicate that an extra X chromosome in Klinefelter patients has adverse effects on the temporal lobes development and function.

Acknowledgement

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