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Neuropsychiatric Disorders in Sex Chromatin Negative Women

By GUNNEL MELLBIN

Chromosomal abnormalities involving the autosomes are nearly always associated with serious defects in intelligence. This is true of the first disease recognized to result from a chromosomal aberration, Down's syndrome (Lejeune, Gautier and Turpin, 1959), and a series of other disorders, including the "cri du chat" syndrome, also first described by Lejeune and his co-workers (1963).

Defects in intelligence also occur in cases of gonosomal aneuploidy, but not always, and then generally in mild form. Several authors, including Mosier, Scott and Cotter (1960), Prader *et al.* (1958), and Forssman and Hambert (1964), have demonstrated mild or moderate intellectual defects in phenotypical men with an XXγ chromosome complement. Likewise, Fraser *et al.* (1960), Maclean, *et al.* (1962) and others have demonstrated that the triple-X pattern is over-represented among mentally defective women. Otherwise, XXγ men and XXX women are often normally intelligent.

Early in the research on the Klinefelter syndrome, Züblin (1953) pointed out that men with the clinical signs of this syndrome are characterized by passivity occasionally interrupted by brief aggressive outbursts. It may be assumed that most of the men Züblin so characterized were sex chromatin positive. Forssman and Hambert (1964) noted an above-average prevalence of sex chromatin positive men among patients at different kinds of institutions for psychiatric care. They found the highest prevalence among criminal or otherwise antisocial men of slightly sub-average intelligence, but also an above-average prevalence among the patients at ordinary mental hospitals, the latter showing a wide variety of disease pictures. Hambert (1964) also noted a presumably above-average prevalence among epileptic men institutionalized for a long time. Nielsen (1964), describing 5 sex chromatin positive male patients at a mental hospital, noted that 2 had psychogenic paranoid psychoses, 2 had character disorders and were unstable in their social functioning and 1 suffered from a manic condition.

Hambert and Frey (1964) observed that sex chromatin positive males showed EEG abnormality far more often than did a control group. Dumermuth (1961) also observed that these men often had an abnormal EEG, but he did not compare their records with those in a control series.

Little has been reported about the neuropsychiatric concomitents of extra X chromosomes in women. Kidd, Knox and Mantle (1963), examining 22 triple-X cases uncovered in mental hospitals and institutions in Scotland, found a wide variety of mental disorders. Eleven of the 22 women were mentally retarded, and these 11 suffered from many more psychotic disorders than a control group of mentally retarded women from the same institutions; 2 of them had epilepsy, and one of these two was psychotic. The authors did not mention any EEG observations.

There are a few scattered reports on neuropsychiatric disorders in women with the Turner syndrome, either the full-blown form of the XO type or the mosaic forms. Wallis (1960), examining 12 young girls with this syndrome, assembled on endocrinologic not psychiatric grounds, noted that 11 had IQ's between 75 and 106 on the Wechsler–Bellevue and Binet–Norden scales, and that 1, a girl of 4, was so retarded that her IQ could not be determined. Van Gemund and van Gelderen (1961), examining 13 sex chromatin negative women, found that 12 had IQ's between 65 and 100 (measured on different scales). Lindsten's monograph of 1963 contains a report of 35 cytogenetically analyzed XO women, 20 tested on the Wechsler–Bellevue scale; 10 of these had

IQ's between 100 and 131, 10 between 81 and 100, and 6 between 71 and 80. Shaffer (1962) concluded, after examining 15 women with negative sex chromatin and 5 showing Turner mosaicism: "With regard to Full Scale IQ, neither group is significantly different from the standardization mean of 100".

Apart from IQ, not much has been written about the neuropsychiatric characteristics of the Turner syndrome. Lindsten found that 28 out of 41 women with clinical signs of the Turner syndrome, or 68 per cent., showed "hearing impairment" on audiometric examination, 20 of purely perceptive type. In his total series of 57 Turner women, 1 had clonic convulsions, 1 enuresis until she was 16, 1 anorexia nervosa, 1 a cyst in the occipital lobe, 1 progressive cerebellar degeneration, and 2 strabismus.

Slater and Zilkha (1961) described a case of Turner mosaicism showing an unusual form of myopathy, and a brief psychotic episode diagnosed as schizophrenia. The patient was the offspring of a first cousin mating. Her IQ (on an unreported scale) amounted to 92.

Milcu *et al.* (1964) described an XO-case with a psychosis diagnosed as schizophrenia.

Pitts and Guze (1963) described a Turner patient with a negative sex chromatin pattern who suffered from anorexia nervosa.

Shaffer (*op. cit.*) noted that the 20 Turner women he examined psychometrically showed "a highly consistent pattern of cognitive strengths and weaknesses similar to that observed in certain types of brain damage".

Dumermuth (1961) reported his EEG findings in sex chromatin negative Turner cases, which he himself said constituted a biased group. Three of the 7 showed "hypersynchronous" abnormalities in their EEG; 1 of these had epilepsy. One showed diffuse dysrhythmia and 1 "passagere fortgeleitete Rhythmen". Two had normal EEG's. Lindsten gave the EEG findings for only 2 of his cases; 1 had an abnormal and the other a normal record.

I shall now describe four Turner cases encountered during psychiatric work. All showed characteristic clinical signs and all showed a negative sex chromatin pattern in buccal smears.

This group is naturally biased in psychiatric respects. But to screen a large population for Turner cases presents great difficulties. For one thing, the condition is rare in the normal population, much more rare, for example than positive sex chromatin in males. Maclean (1964) found a prevalence of 4 per 10,000 in non-selected newborn girls. Another reason is that mosaicism is relatively common in this form of chromosomal aberration, and it is very difficult to know where to draw the line.

Therefore, because the XO pattern is so rare, and because of the neuropsychiatric complications observed in large series of sex chromatin positive men, like those of Hambert, Züblin and Nielsen, the neuropsychiatric complications occurring in 4 cases of the Turner syndrome, biased though they were, seemed to be worth a report.

Case Reports

Case 1

A women of 30, sex chromatin negative, the last five years in a mental hospital.

She is 148 cm. tall and has a childish-looking face. Before substitution therapy was instituted, she had no hair under her arms and very little on her pubes, undeveloped breasts without any palpable glandular tissue, a hypoplastic uterus and no palpable ovaries. Her palatal arch is unusually high; her fingers and toes are long and slender; her nails are unusually small. The proximal section of her right fibula is poorly developed, making her right leg look smaller than her left. She shows a coarse, horizontal nystagmus toward the left. Her muscles are extremely hypotonic.

She went to school for eight years; after that she could not keep up though she was probably of normal intelligence. Until she was 15 she had shown nothing out of the way mentally, except that she was always extremely childish for her age. When she was 15 or 16 a change set in: she got attacks of shaking her arms and legs; she grew nervous and restless; she had spells when she was abnormally apathetic and unenterprising; she got sudden attacks of laughing or weeping; she was unable to concentrate, slept badly and did not want to eat. To begin with, these disorders came on in attacks, but even between attacks she was never well enough to do any work. Eventually the disorders became permanent, and it was concluded that she was suffering from some form of severe brain damage. Five years ago she was admitted to a mental hospital and she has not been allowed out since because it is impossible to predict what she will do. She is now almost completely self-engrossed, uninterested in what goes on around her, almost mute, and emotionally unstable.

EEG's taken when she was 22 and 27 showed mild, non-specific abnormality in both temporal regions, about the same amount on both sides.

Case 2

A woman of 39, sex chromatin negative.

She is 143 cm. tall, looks old for her age, has deformed ears placed far down on her head, heavy occipital region with pterygii colli; until she had a plastic operation, her hair grew far down her back. She shows bilateral cubitus valgus and broad misshapen wrists. She has no hair under her arms, and only a little on her pubes. Her breasts are hypoplastic with retracted nipples in the anterior axillary line; she has a small portio vaginalis, but no palpable uterus or ovaries. She has never menstruated. She shows slight convergent strabismus, marked hyperopia, and spontaneous nystagmus. She is colour-blind, as is also a brother of hers. She has an IQ (Wechsler–Bellevue) of 75.

After leaving school, she stayed home and took care of her old mother, to whom she was greatly attached. Since she was 16 she has had attacks beginning with a sensation of a peculiar smell and ending with brief attacks of lowered consciousness and twitching in her right arm. She has also had a few major epileptic fits accompanied by unconsciousness and tongue-biting at night. When she was 23 she was treated for psychosis at a mental hospital. The psychosis developed as follows: first she became withdrawn and despondent; after a time she began feeling that her end was near, refused to eat and kept throwing herself on the floor; she had hallucinations, saw Satan, heard voices trying to stop her talks with God who had set her apart; she saw worms in her hair and in her stools, and was tortured by "great sins in her breast." She recovered completely a few weeks after her admission and has remained well ever since.

Her EEG is abnormal, showing mild, paroxysmal abnormality slightly more marked in the right temporal region than elsewhere.

Case 3

A woman of 57, sex chromatin negative, admitted to a psychiatric department when she was 54 in connection with an application for a disablement pension.

She is 145 cm. tall, has no hair under her arms and very little on her pubes, and has only a suggestion of breasts. She has never menstruated. Her uterus is very small and no ovaries can be palpated. Her elbows show distinct cubitus valgus and her wrists are deformed.

She is the youngest of four siblings, and after she finished school she stayed at home to take care of her parents. They died when she was 49, and as she was not able to manage by herself she was admitted to an old people's home. She has a distinctly psycho-infantile disposition and is extremely circumstantial and clinging. She was given a premature pension on the grounds of mental disability. She has an IQ (Terman–Merrill) of 86.

Her EEG is abnormal, particularly on the left side where a temporal focus of "sharp waves" was registered.

Case 4

This patient, a woman of 28, will be described in more detail in another article. She is sex chromatin negative, is 149 cm. tall, has no breasts and has never menstruated. She shows bilateral cubitus valgus, her hair grows far down on the back of her neck, and at times pads of oedema appear on her insteps. She has an IQ (Terman–Merrill) of 121.

When she was 17 she was admitted to a psychiatric department for anorexia nervosa. She recovered completely and is now working as a children's nurse.

Her EEG shows paroxysms of activity of the sharp-wave type over the left hemisphere.

Discussion

All four women have an abnormal EEG, and one has frank epilepsy. Otherwise they vary greatly in psychiatric respects. One has a long-standing psychosis of the cerebral lesion type. Another, the one with epilepsy, went through an acute psychotic episode, characterized by a wide range of symptoms, which disappeared leaving no trace. A third has an infantile, adhesive and perseverative constitution, and has been prematurely pensioned on mental grounds. The fourth had anorexia nervosa when she was 17, but got over it and is now quite stable mentally, and works as a qualified children's nurse.

Thus the same was found in these four cases as has been found in sex chromatin positive men—a wide variety of neuropsychiatric disorders, with cerebral dysfunction the common denominator. We know that in what is called the minimum cerebral dysfunction syndrome there are a great variety of psychiatric symptoms all apparently caused by slight cerebral damage. If we consider the four cases of Turner syndrome described above, and the other cases in the literature, we find both a great variety of psychiatric symptoms and clear signs of brain damage shown on the EEG. This suggests that the psychiatric disorders in these cases are the result of cerebral damage.

Summary

The paper reviews the neuropsychiatric literature on the different kinds of gonosomal aneuploidy, and describes four sex chromatin negative women, all with the characteristic

clinical feature of the Turner syndrome. All four had abnormal EEG's and all had had mental disorders of some kind, though these varied greatly in nature. The resemblance to the neuropsychiatric observations in the Klinefelter syndrome is pointed out.

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ADDENDUM

Since this paper was written, a woman of 40 has been admitted to our hospital, showing the clinical Turner Syndrome. She has proved cytogenetically to be an XX/XO mosaic, her IQ is 74–80 and she has an abnormal EEG pattern with moderate, paroxysmal abnormality on both sides, slightly more marked over the right hemisphere.

Gunnel Mellbin, M.D., *Registrar, Psychiatric Department, St. Jörgen's Hospital, University of Göteborg, Sweden*

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