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ORIGINAL PAPER

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The hormonal environment in utero as a potential aetiological agent for schizophrenia

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Abstract There is consistent evidence in the literature that the foetal neurodevelopmental period is crucial for the genesis of schizophrenia later in adult life. There are also strong indications that the schizophrenic illness has sexually dimorphic features. A hypothesis consistent with both findings is that sexual hormones may act as aetiological agents for schizophrenia during the foetal period influencing the neurodevelopment in a differential way in males and females. The aim of this study is to verify this hypothesis exploiting the correlation between fingers' length in adults and hormonal concentrations in utero, which has been demonstrated in previous studies. More specifically, the literature shows that the lengths of the second and fourth finger in adults are proportional to the foetal concentrations of respectively oestrogens and androgens. When the sample of patients suffering from schizophrenia analysed in this study was compared with healthy subjects, it was observed that the average length of the second digit in the female schizophrenic sample resulted significantly shorter than in the female controls. There was no significant difference when the male schizophrenic sample was compared with male controls. The result of the study is, therefore, compatible with the hypothesis that oestrogenic hormones protect female foetuses from damage during the neurodevelopment in utero and ultimately give more benign characteristics to the schizophrenic illness in women.

Key words schizophrenia · hormones · testosterone · estrogen · gender

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Introduction

There is consistent evidence from the literature that events during the foetal neurodevelopmental period are crucial for the genesis of schizophrenia later in adult life [20, 22, 27, 29]. There are also strong indications that the schizophrenic illness has sexually dimorphic features [33]. A hypothesis consistent with both findings is that sexual hormones may act as aetiological agents for schizophrenia during the foetal period influencing the neurodevelopment. They would affect males and females in a differential way because of the different average concentration in the two sexes.

Due to the infeasibility of measuring directly foetal blood concentrations of sexual hormones and then undertaking a very large longitudinal study over decades, it has been decided instead to carry out a retrospective study measuring the length in adults of the second and fourth digits, which previous studies have shown to be correlated to the levels of sexual hormones in the same individuals previously in foetal life [24–26, 44].

Method

Study design

The aim of the study is to verify whether there is a correlation between the concentrations of sexual hormones, especially oestrogens and androgens, in utero, and the development in adulthood of schizophrenia. A longitudinal study is unrealistic for several reasons. First

of all, it would imply direct measurements of the plasma levels of sexual hormones in a large number of foetuses, and these measurements cannot be done without endangering the pregnancy. Even if this problem were overcome, a longitudinal study would involve carrying out these measurements in thousands of foetuses and following up the subjects into adulthood for decades. Schizophrenia is in fact a relatively rare disorder, having a lifetime prevalence below 1%, and its onset is seldom before the late teens.

For the above reasons, it was decided to undertake a retrospective study, which allowed selecting a sample of patients already known to suffer from schizophrenia, thus overcoming the problems described earlier. A retrospective study, therefore without measuring directly the hormonal concentrations in the foetal blood, has been possible thanks to the fact that the length of the second and fourth finger in adults has in previous studies shown to be correlated to the concentrations of respectively oestrogens and androgens in utero [24–26, 44].

Participants

The sample examined in our study has been selected amongst inpatients, day-patients and outpatients living in the county of Sussex, United Kingdom, aged between 18 and 65 and fulfilling ICD-10 [45] criteria for schizophrenia (F.20). The patients are not related to each other. The control population was randomly chosen amongst healthy members of staff working for the local Health Authority. Their healthy status was determined through a questionnaire. The controls are representative of the same geographical area as the patients and match the sample for sex and age distribution. In the selection of both the schizophrenic and the control population, the presence of rheumatological or other physical disorders, which could influence the length and the shape of the fingers and a history of learning disabilities, were exclusion criteria. Excluded from the control population were also those subjects with a history of mental illness and those with a family history of schizophrenia. Patients and controls were explained the rational of the study, both verbally and in writing, and they signed a consent form. The total number of subjects studied was 119, with 27 male controls, 35 male patients, 32 female controls and 25 female patients, giving a reasonably balanced design, where in this context balance refers to the study having roughly equal size and power for both cases and controls in the male and female group. The sample sizes were determined by resource constraints.

Measurements

The measurement of the digits' lengths was made with a digital calliper precise to a tenth of the millimetre. The digits were measured from the tip to the proximal crease. It was decided to measure the digits in the right hand because rings, which are usually worn on the left hand, can cause measurement difficulties by covering the digits' proximal creases. The first finger (thumb) was not included in the analysis because, due to its curved shape, it is difficult to standardise the measurements. All the measurements were performed by the same researcher, RD, to avoid issues of inter-rater reliability. RD was blind to the hypothesis at the time of the measurements.

Statistical analysis

The data were first explored using graphical techniques to assess distributional assumptions and to see if there were any potentially highly influential outliers. In order to take into account the size of the patient, a potential confounder when considering male and female subpopulations, we normalised finger lengths by using the ratio of the subjects' heights and finger lengths.

After stratifying by gender and illness, we used the Welch two-sample t-test to test for potential differences in the normalised finger lengths across subpopulations. For each finger and gender combination, the control and patient populations were compared. The null hypothesis always tested was one of no difference between subpopulations, while the alternative hypothesis used to assess the p-value was two-sided. All calculations were done using the statistical package R (http://www.r-project.org).

Results

Table 1 shows the detailed results of the analysis, with a summary of the data in Table 2. The null hypothesis of no difference was rejected against a two-sided alternative with a p-value of 0.017 for the second finger for female subjects and was not rejected in all other groups.

Fig. 1 shows four boxplots that illustrate the distribution of height to finger length ratio for the second and fourth fingers across both the male and female subpopulations for both patient and control groups. The case that shows a significant difference is in panel (b) with an

Table 1 Results of using t-tests to test the hypothesis of no difference in mean between the control and patient groups across subpopulations. Finger lengths are normalised by considering the subjects' height to finger length ratio

Finger	Gender	t-statistic	p-value
Second	Male	−0.636	0.527
Second	Female	−2.445	0.017
Middle	Male	−0.710	0.481
Middle	Female	−0.194	0.848
Fourth	Male	−0.442	0.661
Fourth	Female	−1.972	0.054
Little	Male	−1.435	0.158
Little	Female	−1.523	0.135

Table 2 Summary statistics for the actual length of each figure (mean and standard deviation) before normalisation for each group

	Mean (mm)	SD (mm)
Males/controls		
Index	71.64	4.56
Middle	79.73	5.15
Ring	73.17	4.60
Little	59.42	3.53
Males/patients		
Index	70.13	5.11
Middle	78.00	6.16
Ring	71.93	6.26
Little	57.33	6.04
Females/controls		
Index	68.21	4.69
Middle	73.60	8.35
Ring	68.70	5.00
Little	54.88	4.44
Females/patients		
Index	64.57	4.54
Middle	70.80	5.06
Ring	65.26	5.80
Little	52.18	6.01

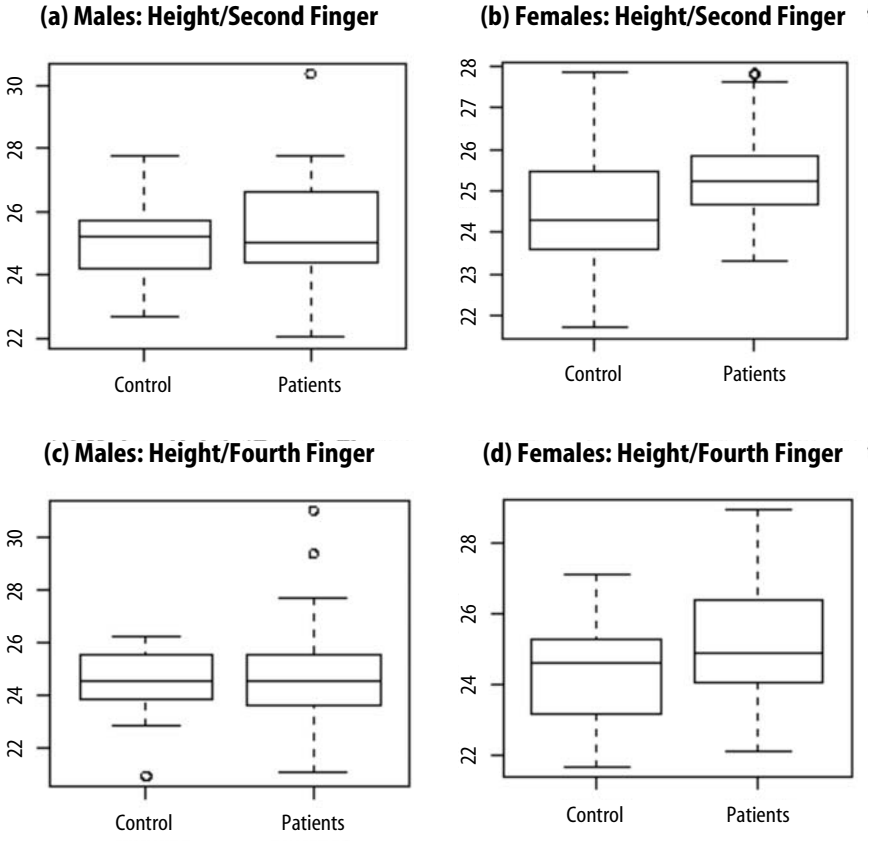

Fig. 1 Boxplots showing the distributions of the normalised height to finger length ratio for (**a**) male controls and patients for the second finger (**b**) female controls and patients for the second finger (**c**) male controls and patients for the fourth finger and (**d**) female controls and patients for the fourth finger

increase in the height to finger length ratio corresponding to relatively shorter finger lengths in the patient group.

The female schizophrenic population showed a lower average height than the female controls, though this difference did not reach statistical significance.

Discussion

This study shows that the length of the second digit, when compared with body size, is influenced by the diagnosis of schizophrenia and by the sex of the individual. There is in fact a significant difference between female schizophrenic patients and female controls when looking at the proportion between the length of the second finger and their height. Female schizophrenic patients' second fingers are on average significantly shorter in proportion to their height when compared with female controls. There was no significant difference in females when the same method was applied to the other digits. There was also no significant difference in any of the digits, including the second and the fourth, when the same method was used comparing male schizophrenic patients and male controls.

Several studies have shown that the length of the second digit in adults is directly proportional to the average plasma oestrogen concentration in the individual. In the same fashion, the length of the fourth finger is directly proportional to the average plasma concentration of androgens [24–26, 44].

The fact that the proportion between the length of the above two digits (second : fourth) is already fixed around the thirteenth week of intrauterine life [9] has led to the conclusion that the length of the two digits is also representative of the foetal concentrations of oestrogens and androgens. Their measurements therefore represent a "smoking gun" of what were the concentrations of an individual's sexual hormones in utero [24–26, 44].

This methodology is very useful because direct data of the concentrations of sexual hormones in utero are not available. Most of the data derive in fact from umbilical cord samples, therefore relevant only to the latter stages of intrauterine life. It is not even known in what proportion the sexual hormones present in the foetal circulation are produced by the foetus or by the mother.

It is reassuring that the phenomenon observed in our study is statistically significant only for the second finger, because it is one of the two digits which have shown to have a correlation with the foetal concentrations of sexual hormones [24–26, 44]. If the difference was also significant in other fingers it could have signified the presence of some artefact or just the presence of altogether smaller hands in schizophrenic female patients.

It is also reassuring that the result is significant in females and not in males. This supports a genuine difference in finger length, and not just an anomaly of the

hand creases. Abnormal hand creases are in fact known to be present in schizophrenic patients, but with no gender differences [7]. Therefore, if the difference in digits' length between schizophrenic patients and controls were due to anomalies of the creases influencing the measurements, these differences would be present in both sexes, and not just in females.

The average height in our female schizophrenic sample is lower than in the female controls. This finding is not surprising, being supported by a robust body of literature that suggests a lower average height in patients suffering from schizophrenia when compared with the general population [31].

Therefore, the positive result cannot be due to the height of the subjects acting as a confounder. If anything the lower average height in the schizophrenic sample will lead to an underestimation of the size of the phenomenon.

The study shows that in women there is an inverse correlation between the plasma concentrations of oestrogens in utero and the risk to develop schizophrenia. The same is not true for males in which the risk does not seem to be related to the hormonal situation in utero.

Based on the results of this study, the hormonal component, present in the foetal circulation, that influences the risk of schizophrenia in females is unlikely to be of trans-placental origin, but is probably produced by the foetus herself. If it were due to the mother's production of hormones, it could not be explained why only female foetuses are affected. The sex difference suggests instead a hormonal difference driven by the foetal sex.

The above results are consistent with recent studies that have shown a strong protective influence of oestrogens during the neurodevelopment. Testosterone instead does not seem to have any significant influence, positive or negative, on neurodevelopment [10].

This important role of oestrogens in the aetiology of schizophrenia is consistent with the literature that shows a sexual dimorphism in the illness. Typically, for instance, the age at onset in schizophrenia is earlier in males than in females. Male patients' age at onset peaks between the late teens and the early twenties, while the peak of onset for female patients is significantly later, between mid-twenties and mid-thirties [5, 13, 14, 21].

Despite most "classical" studies indicating an equal incidence of schizophrenia between the two sexes, some recent studies have challenged this concept, indicating a higher incidence of schizophrenia in males [6, 16, 17, 28].

It is also regularly suggested in the literature that there are differences in the clinical presentation between sexes. Female patients, when compared with males, have a higher incidence of paranoid and affective symptoms and a lower likelihood to develop a disabling negative syndrome [1, 23, 32, 40].

It is also reported in the literature that women have a better prognosis and response to pharmacological treatment when compared to men [3, 15, 37, 38, 42].

Epidemiological studies and animal experiments are concordant in showing an anti-dopaminergic effect of oestrogen hormones. It has, therefore, been hypothesised an anti-psychotic effect of oestrogens [12].

On the other hand, an increasing body of evidence suggests that the sexual dimorphism in schizophrenia is also based on more structural differences. There are in fact regular indications coming from the literature that there are differences in the structure of the brains of schizophrenic patients when compared with normal controls. Among these differences, the more constantly replicated are an enlargement of the brain ventricles [8, 39, 41] and reduction in volume of certain areas in the temporal lobe [11, 19, 38].

These differences are likely to have a neurodevelopmental origin because of the lack of gliosis that otherwise would be present if they were due to damage in extra-uterine life [34].

Several studies indicate that these structural anomalies are present either only in male patients or at least with a greater significance in male schizophrenics [2, 4, 18, 30, 35, 43].

Conclusions

It is therefore possible, on the basis of the results of this study, to develop the hypothesis that the more benign characteristics of the schizophrenic illness in females are due to the neuro-protective influence of oestrogens in utero. The presence of oestrogens can probably protect from traumas in utero which may lead to schizophrenia in adulthood, or at least limit the damage. In those females who have a lower than average concentration of oestrogens in utero and/or adult life, this protection is less effective.

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