Clinical Features of Schizophrenia in a Woman with Hyperandrogenism

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Submitted: May 6, 1996
Accepted: September 27, 1996

Ample evidence supports sex differences in the clinical features of schizophrenia. In this regard, estrogen may contribute to later onset and less severe course of illness in women. Direct investigation of hormonal status in schizophrenia is extremely difficult. The present report documents the clinical features of schizophrenia in a young woman with long-standing hyperandrogenism related to polycystic ovarian disease. We postulate that hyperandrogenism contributed to a relatively early onset, olfactory dysfunction, and other clinical features of schizophrenia more commonly associated with men. Additionally, acute estrogen depletion following cessation of oral contraceptives may have precipitated psychosis, while recommencement of oral contraceptives could have contributed to subsequent improvement in symptoms.

Key Words: schizophrenia, sex differences, olfaction, hyperandrogenism

INTRODUCTION

Empirical evidence suggests systematic differences in clinical features between women and men with schizophrenia. Men are significantly younger at symptom onset and at 1st psychiatric hospitalization (Eaton 1985; Goldstein 1995) and are more likely to manifest negative symptoms, whereas women are more often characterized by affective and paranoid symptomatology (Lewine 1988; Haas and Sweeney 1992). Severity of illness expression in women is less debilitating than in men during the 1st decade following onset (Thara and Rajkumar 1991; Leff and others 1992) and approximates that of men in subsequent years, once any given cohort passes through menopause (Seeman 1996). Some, but
not all, studies of brain morphology reveal a higher prevalence of qualitative abnormalities in men (Raz and Raz 1990; Lewine and Seeman 1995). Although evidence for sex differences in neuropsychological functioning is mixed (Haas and Sweeney 1992; Walker and others 1992; Goldberg and others 1995), olfactory deficits are more consistently demonstrated in young male than young female patients with schizophrenia (Kopala and others 1989, 1992). Finally, men tend toward a less favorable outcome when compared to women, both in the short and the long term (Seeman 1989; Castle and others 1995).

Hormonal influences on the development of schizophrenia in both sexes were postulated (Seeman and Lang 1990). Specifically, estrogen was suggested to be protective and to contribute to the later age of onset and less severe course of illness observed in women—at least until menopause, when estrogen levels fall. In this context, postmenopausal women with schizophrenia who lack the protection of estrogen have olfactory identification deficits, whereas younger women with schizophrenia most frequently have intact olfactory function (Kopala and others 1995). The estrogen hypothesis was further supported by studies indicating an antidopaminergic effect of estrogen that may enhance the effectiveness of antipsychotic medication (Häfner and others 1993; Di Paolo 1994; Riecher-Rössler and others 1994). There are few direct investigations of hormonal status in schizophrenia (Dalton 1959; Hallonquist and others 1993). The present case of schizophrenia in a woman with relative hypoestrogenism and long-standing hyperandrogenism provided an interesting opportunity to determine if features of schizophrenia more commonly observed in males might occur in this individual.

CASE REPORT

M was a 23-year-old, single, unemployed Caucasian woman living at home with her parents. She was hospitalized for the 1st time because of increasing isolation and aggression directed toward her family.

M was the product of a full-term, uncomplicated pregnancy and was described as an awkward and extremely shy child. She was school-avoidant, had numerous somatic complaints, and had few friends. In adolescence, she did not date or socialize, and she struggled to obtain passing grades. Through the latter part of secondary school she was increasingly isolated, spending long periods in her room; she was 1st assessed for "emotional" problems at age 18.

Counseling was not perceived to be helpful by either M or her family. After completing grade 12, M was employed as a sales clerk for a few weeks at a time, but she was unable to continue because of stress.

M was investigated for hirsutism and oligomenorrhea at age 18. Slowly progressing hirsutism and irregular menses, occurring at 5- to 9-week intervals, had been present since menarche at age 13. Hormonal studies revealed elevated total testosterone level (3.9 nmol/L, Normal 0.35 to 2.43 nmol/L) and decreased sex hormone binding globulin (less than 1 nmol/L, Normal 30 to 90 nmol/L), yielding a markedly elevated free testosterone index. A reduced serum estradiol level (82 pmol/L, Normal 110 to 1290 pmol/L) and an anovulatory progesterone level (less than 1 nmol/L) were also documented. All other laboratory findings, including a complete blood count, renal, and thyroid function tests, were unremarkable. M received a prescription for spironolactone and oral contraceptives. She took the latter for approximately 2 y, but cost prohibited her obtaining the spironolactone beyond a few months. Following discontinuation of oral contraceptives at age 20, M first developed psychotic symptoms and received a diagnosis of paranoid schizophrenia as an outpatient. Antipsychotic medication was recommended, but M was noncompliant.

Her mother suffered from "nervousness" and took minor tranquilizers. A maternal grandfather was described as moody and a loner. M’s 2 older siblings were functioning well.

On assessment following admission, she exhibited prominent negative symptoms including blunted affect and emotional withdrawal, along with auditory hallucinations, persecutory, paranoid, and religious delusions, ideas of reference, no insight, hypersensitivity to noise, hostility, and combativeness (Figure 1). There was no history of substance abuse. She met DSM-IV criteria for an Axis I diagnosis of schizophrenia, undifferentiated type.

Physical examination of the patient at admission indicated a weight of 72.2 kg, a height of 165 cm, and a body mass index of 27 kg/m², which is consistent with mild obesity. Significant hirsutism was present, with male-pattern facial...

![Figure 1. PANSS scores at baseline, 8 weeks, and 6 mo. Combined oral contraceptive pill (OCP) initiated at 10 weeks.](image-url)
and pubic hair distribution and well-muscled, excessively hairy arms and legs. The Ferriman-Gallwey score, an objective measurement of hirsutism (Ferriman and Gallwey 1961), was 22 (upper Normal limit of 9). Previous and repeat pelvic examination revealed a small, normal uterus and 2 apparently normal ovaries, confirmed by ultrasound. The external genitalia and vagina were normal. A reproductive endocrine evaluation revealed a high normal testosterone (2.1 nmol/L), elevated androstenedione (12.8 nmol/L, Normal 1.7 to 9.4 nmol/L), and an elevated luteinizing hormone:follicle-stimulating hormone ratio (30:13 IU/L), consistent with a diagnosis of polycystic ovarian disease. The serum progesterone concentration remained in the anovulatory range on menstrual cycle day 41. Sex hormone binding globulin and free testosterone index measurements were not available.

M was a nonfamilial left-lander with sinistrality confirmed with the Edinburgh Handedness Inventory (Oldfield 1971). Neuropsychological assessment confirmed with the Wechsler Adult Intelligence Scale—Revised, Wisconsin Card Sorting Test, Trails A and B, Stroop Color—Word Test, Peabody Picture Vocabulary Test, Design Fluency, Benton Naming, and Controlled Oral Word Association Test (form C, administration A) indicated perseveration, decreased psychomotor speed, decreased verbal and figural fluency, mild contamination and confabulation in free recall, and overall borderline intellectual functioning. Receptive language, visuoconstructual abilities, and absolute levels of learning were within the low average range. The pattern of neuropsychological compromise was suggestive of diffuse brain dysfunction, likely most pronounced in prefrontal regions, with temporal and parietal regions less compromised.

Olfactory testing employing both identification (University of Pennsylvania Smell Identification Test [UPSIT]) (Doty and others 1984) and acuity (threshold) tasks were completed unirhinally, using methods described in detail elsewhere (Kopala and others 1995). Despite intact acuity for both nostrils, M had a left nostril olfactory identification deficit (UPSIT right = 18/20; left = 13/20).

Neurological examination and electroencephalogram were normal. A computed tomography scan showed some widening of the trigone—occipital horn area of the lateral ventricles, associated with biparietal sulcal widening. No abnormalities of the periventricular white matter were noted. A magnetic resonance imaging scan was performed with sagittal, coronal and axial sections. Aside from confirming the computed tomography scan findings of biparietal atrophy, no additional abnormalities were detected. Specifically, the gyri rectus and olfactory sulci were of normal configuration.

All initial investigations and diagnostic interviews were completed prior to administration of antipsychotic medication. Treatment with risperidone monotherapy (initial dose of 2 mg) was initiated and improvement noted. The dose was increased to 3 mg/d after 1 week. She experienced mild akathisia for several days, which abated without treatment. After 8 weeks, M was discharged home receiving only risperidone 3 mg/d and was seen regularly as an outpatient. She received no other antipsychotic medication. A combined estrogen/progesterone oral contraceptive (desogestrel-ethinyl estradiol) (Marvelon) was initiated approximately 2 weeks after discharge. The Positive and Negative Syndrome Scale (PANSS) (Kay and others 1987) ratings were repeated at discharge and after 6 mo (see Figure 1).

**DISCUSSION**

This case documents the clinical features of schizophrenia in a young woman with long-standing hyperandrogenism related to polycystic ovarian disease. This condition resulted in mild obesity, hirsutism, and oligomenorrhea and may have contributed to the clinical expression of illness. Lewine and Seeman (1995) recently reviewed sex differences in schizophrenia. Regarding endocrine factors, they point out that androgens are aromatized to estrogens in both men and women, interact in a complex fashion with numerous other hormones and genes, and act at receptors that are uniquely distributed in the 2 sexes. From a clinical perspective, numerous studies indicate that schizophrenia in men is characterized by relatively early onset, more frequent history of birth and pregnancy complications, prominent negative symptoms, compromised central nervous system (CNS) function, and poorer response to typical antipsychotic medication. By contrast, schizophrenia in women is characterized by later onset, fewer pregnancy and birth complications, prominent positive symptoms, less impairment of CNS function, and better response to treatment (Seeman and Lang 1990; Lewis 1992; Lieberman and others 1992; Castle and others 1993).

In the present case, although the birth was not reported to be complicated, early abnormal development was noted in the description of an awkward, unaffectionate, extremely shy child with social and academic problems at school. Frank psychosis may have been precipitated by acute estrogen depletion following cessation of oral contraceptives at age 20. M had prominent negative symptoms at initial presentation, and these symptoms responded modestly and more slowly to treatment, also consistent with findings for men with schizophrenia (Haas and Sweeney 1992). Chouinard (1994) suggested a superior response to risperidone in women with schizophrenia, whereas men apparently had a better outcome when treated with clozapine. Kopala and others (1996) reported improvement in positive, negative, and general symptoms in first-episode patients with schizophrenia treated with a mean dose of 4.7 mg (range 2.0 to 8.0 mg) of risperidone. The women in Kopala and others’ (1996) study received lower doses of risperidone than did the men (3.2 mg versus 5.2 mg). Subsequent improvement in the current patient’s symptoms may have resulted from the addition of an estrogen-containing oral contraceptive.
Neuroimaging demonstrated structural brain abnormalities. Compromised CNS function was suggested by neuropsychological and olfactory assessments. Because olfactory identification may serve as a probe for assessing the functional integrity of orbital frontal, temporal, or thalamic brain regions, this finding is of particular interest. Unlike most younger women with schizophrenia who have been studied to date, this woman had olfactory identification deficits with intact acuity. This is more consistent with previously reported data for younger men with schizophrenia (Kopala and others 1989, 1992, 1994). Olfactory identification deficits are reported for older, pre- and postmenopausal women with schizophrenia, however, suggesting a modulating role for estrogen (Kopala and others 1995).

M was a nonfamilial left-hander. Her left-handedness may have resulted from brain dysfunction within the left hemisphere. Specifically, a biological right-hander could become left-handed because of relative left hemisphere dysfunction. In keeping with this finding, M had a left nostril olfactory deficit, suggesting more marked left hemisphere abnormalities (Good and others 1995). Greater left than right hemisphere abnormalities have been reported in schizophrenia (Shenton and others 1992).

The present case supports a model of schizophrenia in which circulating sex hormones contribute to the developmental pattern and clinical presentation of illness. Parallel studies of endocrine function and clinical features of schizophrenia in women may contribute to understanding those aspects which modify the expression of illness.

ACKNOWLEDGEMENT

WGH was a scholar of the Medical Research Council of Canada.

REFERENCES


