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Chromosomal Aberrations in a Patient with Severe Psychopathology

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The case of a female patient showing aggressive, compulsive, destructive behaviour, ritualistic faecal smearing, and hyperactivity is presented. The behaviour is long standing, therapy-resistant, and its aetiology is unknown, although it is seemingly associated with chromosomal abnormalities secondary to abnormal plasma factors.
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An abstract on this patient has been previously presented (Wetterberg *et al*, 1988). This more detailed account is made in the hope of eliciting suggestions as to aetiology and treatment.

Case report

The patient shows compulsive, violently aggressive and destructive behaviour, faecal smearing, and hyperactivity. These have remained stable. Her daily routine is rigid and ritualistic and it is nearly impossible to divert her from it. She awakes, smears faeces on the wall, tears her underclothing, and engages in postprandial spitting and vomiting. She walks for 4–5 hours in an enclosed yard while ordering minor changes in diet. She writes two or more letters a day, frequently signed with her father's name or the names of others. She is generally less aggressive at night, goes to bed early and sleeps well regardless of daily events. Her violent behaviour may be preceded by frustration but often occurs without obvious cause. She shows unusual strength during outbursts, often requiring several men to restrain her. She has inflicted severe injuries, including fractures, on others. She rarely attacks her parents but destroys their possessions when angry. Her behaviour seems under some control since she accepts some staff members and is not violent during medical examinations or dental care but she often requests to be restrained, lest she "get an impulse" and injure someone, suggesting uncertain control of her emotions.

Her illness is of early onset and she has never been symptom-free. She has never shown symptoms of disturbed consciousness, confusion, disturbed speech, seizures or other focal neurological signs, hallucinations, autism, depression, or memory disturbance, nor has there been any sign of deterioration. Her vision and hearing are normal and she seldom complains of headaches.

The age of onset is unclear. Her mother claims detecting abnormally destructive, aggressive, and anxious behaviour as early as her daughter's eighth month, but other reports suggest normal early behaviour except for impulsive aggressive behaviour towards children her own age or younger outside the home. Aggressive, destructive, unpredictable, and compulsive behaviour became more manifest at the age of three upon the birth of her eldest brother. She received psychiatric counselling the following year and was admitted for diagnostic evaluation at the age of 7. Her behaviour deteriorated and she has been an in-patient since the age of 10. Eating disorders began at age 20 and included postprandial spitting and vomiting. These have persisted. Her height is 171 cm and her bodyweight presently ranges between 40 and 45 kg. Since the age of 20 she has tried a series of diets, avoiding meat, sugar, fat, wheat, etc., without benefit.

The patient expresses interest in her problem, but lacks insight. She says "I cannot do anything about my impulses. I get a feeling in my stomach, a tension, a fear. I have to get rid of that tension. My wits are unleashed at that moment". When asked about a future outside the hospital she responds with a stereotypic desire for "a husband, a home and a poodle".

Family history

The father was reportedly aggressive, destructive, impulsive, and antisocial as a child. At the age of 38 he experienced unconsciousness and an electroencephalogram showed epileptic activity in the frontotemporal regions of the left cerebral hemisphere. He was treated with phenytoin and the

antiepileptic medication was terminated 3 years later after a normal electroencephalogram. Several members of the father's family reportedly have 'impulsive' features in their personality.

The mother has chronic, recurrent thoracolumbar back-pains and a primary, benign hypertension. She has developed recurrent depressive episodes during the last few years and has been treated with antidepressants. The mother's sister was reported to have been aggressive and destructive as a child. Several members of the mother's family have arteriosclerosis-related diseases and some have non-toxic goiter. A cousin has Parkinson's disease, the daughter of a cousin has had severe aplastic anaemia, the son of an uncle has had surgery for transsexualism, and a son of her cousin has committed suicide.

The patient has two brothers, 3 and 10 years younger than her. The elder has always been healthy. The younger had neonatal jaundice. At the age of 10 he had a head trauma and a short loss of consciousness following an accident, without signs of sequela. At 16 he experienced a period of severe anxiety and existential brooding.

Diagnostic considerations

The patient does not seem to fit recognised categories of psychiatric disorder and different rating systems yield different assignments. She fits most closely with atypical psychosis by DSM-III and major affective illness with psychosis by DSM-III-R (American Psychiatric Association, 1980, 1987). She does not fit any of the categories of the diagnostic systems devised by Feigner, Schneider, or the French system of Pichot (1984). Her illness has been variously diagnosed as childhood psychosis; symbiotic psychosis *ad modum* Margret Mahler; chronic schizophrenia with obsessional and compulsive features; hysterical syndrome with possible organic components; malignant obsessional syndrome; *persona pathologica schizoides, immatura et explosiva*; severe emotional developmental disturbance; grossly amplified MBD (minimal brain dysfunction); anorexia nervosa; severe contact disturbance; and epileptogenic disorder.

Treatment trials

Among the therapies tried have been:

(a) psychotherapy (intensive regression therapy, supportive therapy and family therapy)
(b) psychopharmacology with most of the oral and injectable neuroleptic drugs registered in Sweden (clozapine, barbiturates, benzodiazepines, carbamazepine, cyclic antidepressants, anticholinergics, vitamin B and C, antihistamines, phenytoin, amphetamine, and lithium); dosage is complicated by frequent vomiting, and plasma concentrations of psychotropic drugs have not been monitored
(c) physiotherapy
(d) occupational and recreational therapies
(e) such irregular methods as cold showers, forced laxation, starvation, and fever therapy.

None have been useful. The patient's severe behaviour problems cause great management problems. During the last seven years she has been kept as a single patient on an isolated ward staffed by a total of 15 mental health assistants. She lives in two rooms furnished only with one bed, a concrete support elevated from the floor and covered with a rubber mat. She keeps her few personal belongings in plastic bags. Currently she is on long-term psychotherapy combined with clomipramine 75 mg/day and phenytoin 100 mg/day.

Patient history

The patient was born to a 30-year-old mother. Pregnancy was uneventful except for three weeks of nausea early in pregnancy treated with an unknown medication. Birth weight was 3.04 kg and length was 50 cm, with a skull circumference of 31 cm. The neonatal period was medically normal. The patient was breast fed for only a few months due to insufficient lactation. Psychomotor development was normal. She received routine vaccinations. Three variola vaccinations were given because the patient did not develop the proper skin response.

Prominent symptoms in her youth, as now, were aggressiveness, anxiety, urine and faecal smearing combined with excessive cleanliness, stereotypic perseverations, and persecutory hostility. She reportedly enjoyed art and writing. She speaks and writes Swedish, German and some Italian. Several psychologists who have tried formal IQ testing have reported an average or better intellectual level although it has not been possible to carry out complete psychological tests due to the patient's condition.

Menarche was at 14 and secondary sexual characteristics developed normally. Her menstrual cycle has been irregular since its onset and she has had continuous, secondary amenorrhoea since the age of 20, probably because of diet and psychopharmacological medication. She has never been pregnant and gynaecological examinations have been normal.

The patient had short periods of constipation during childhood, a fracture of the right forearm at the age of three which healed without sequela, and a variety of infections. These included (age in years given in parentheses): acute laryngotracheities (2), bilateral parotitis (10), varicellae (11), external otitis in right ear (22), distal urinary tract infection (22), bilateral tinea inguinalis (22), and recurrent right gluteal ulcers and fever due to infection (22). She had signs of reversible hepatic dysfunction (elevated serum alanine-aminotransferase) at the ages of 14 and 21 years attributed to side-effects of neuroleptic medication. At 22 she had an episode of polydipsia without obvious cause and with a normal blood sugar level.

Her weight has varied over the years from 90 kg at ages 18 and 22 to 36 kg at the age of 24. The weight gains were attributed to psychopharmacological side-effects. She has had severe nightly bruxism. Interestingly, she has undergone dental procedures without requiring analgesia. Slight arterial hypertension without concomitant changes in heart frequency was noted on a few occasions of agitation.

Recently the patient has developed a minor eczema of hands and feet of unknown origin, recurrent infections

Table 1
Cellular hyperdiploidy in the patient (P) and healthy controls (C)

	Tissue source	Culture medium		Replicates: *n*	Total cells counted: *n*	Hyperdiploidy: %
	lymphocytes	plasma	serum			
1.	P	P	-	2	74	19
2.	P	C	-	2	49	28
3.	C	P	-	7	235	8
4.	C	C	-	2	54	17
5.	P	-	C	6	186	4
6.	Bone marrow cells (P)			1	23	26
6a.	Bone marrow cells (C)			60	700	0.6
7.	Cultured fibroblasts (P)			1	30	0
7a.	Cultured fibroblasts (C)			50	5000	0

Chromosome analysis was carried out on cells from phytohaemagglutinin (PHA) stimulated lymphocytes cultured in Parker 199 medium (National Bacteriological Laboratory, Stockholm, Sweden) with 20% (v/v) human AB-serum or plasma supplemented with penicillin 100 IU/ml, streptomycin 100 μg/ml and PHA. Cultures were incubated for 72 h at 37°C and 90 min before the end of the culturing time, Colcemid (CIBA), 0.1 μg/ml (2.7×10^{-7} M), was added. Conventional air-dried slides were Giemsa stained for analyses of chromosomal aberrations (Gustavson *et al*, 1983) recorded in accordance with WHO recommendations (Buckton & Evans, 1973; Nordenson, 1979). Sixty or more cells were analysed in most cases. Lymphocytes cultured in AB-serum and plasma were also analysed. Cells from a skin biopsy from the patient were cultured for chromosome analyses according to Rojanasakul *et al* (1985). Short-term culture of bone marrow cells (24-h incubation without PHA in McCoy 5A medium) were used for chromosome studies. (Reference for 6a Benson *et al* 1988; for 7a Gustavson K-H (personal communication).)

Table 2
Chromosomal defects in normal, control lymphocytes cultured in medium[1] with specific plasma protein fractions added from the patient

			No. of cells analysed with chromosome number						
	Plasma fraction	Mol weight: kD	44	45	46	47	48	49	Chromosomal abnormalities
1	Dialysate	<12	2	5	37	3	-	1	In four cells: 46,xx + one fragment. In one cell: 49,xx − one chromosome 8 + two marker chromosomes + one ring chromosome.
2	Dialysate	<3.5	-	2	48	-	-	-	0
3	Dialysate	>12	-	5	44	-	-	-	0
4	Dialysate	>3.5	1	2	46	1	-	1	In one cell: 46,xx + one fragment. In one cell: 49,xx + one chromosome 3 and one chromosome 5, one chromosome 9 + two marker chromosomes.
5	Intact plasma			3	46	-	-	-	In one cell: 46,xx + one fragment.
6	Medium only		-	3	43	2	-	-	0

1. For experiments 1–4, 8 drops of heparin-blood + 2 ml of the fraction (for experiment 5, 2 ml intact plasma) incubated for 72 hours in a culture medium containing 1 ml AB-serum, 4 ml Parker 199, 0.1 ml penicillin–streptomycin, 0.2 ml phytohaemagglutinin. Plasma was dialysed for 24 hours against an excess of 0.1 M phosphate buffer, pH 7.4. Dialysis tubings with two different molecular weight (MW) cut-offs were used, 3.5 and 12 kD. The dialysate was lyophilised and desalted. The remainder was dissolved in sufficient 0.1 M phosphate buffer, pH 7.4, to restore the original dialysed plasma volume.

around fingernails, recurrent mycosis in the groin, probable Raynaud-phenomenon in the fingers on cold exposure, and slow rate of growth of scalp hair. The patient has shown a slight polyuria including nocturia 2–3 times a night. Electroencephalograms have consistently shown "non-specific, bilateral, symmetrical dysrhythmia". Serological tests for syphilis and toxoplasmosis have been negative.

Tests

Both general procedures and specialised cytogenetic methods have been used.

(a) General procedures: the status of major metabolic pathways and of the endocrine, immunological, sensory, and organ systems were examined with a battery of chemical, physiological, electrophysiological, radiological, and tomographic tests over the years (see below).

(b) Cytogenetic studies: in addition, cytogenetic studies were carried out on cultured peripheral blood lymphocytes, gluteal skin fibroblasts, and pelvic bone marrow cells from the patient and on lymphocytes from normal controls (see Tables 1 and 2).

Several tests were also carried out on tissues from family members. Some routine blood and urine laboratory tests

were performed on the patient while on a regular daily medication of 3 mg trifluoperazine, 2 mg fluphenazine and 150 mg clomipramine so as not to alter her stable condition. Later it was possible to reduce medication to the drug-free condition for one month, when routine laboratory tests were run. Medication was reinstated because of increased anxiety and management problems.

Results

The results of the clinical examinations and the cytogenetic studies are summarised below.

General

Intermittent systolic/diastolic hypertension without changes in heart frequency or obvious concomitant change in psychopathology; intermittent reduction of serum osmolality; slightly defective renal tubular function; and "low renin, low aldosterone hypertension and abnormal cortisol metabolism" (Fisher *et al*, 1982) were found. The patient also showed carotenaemia of parts of the skin; generalised hyperostosis of the calvarium (Reeder & Felson, 1975); slight hypocalcaemia and hypovitaminosis D; and gelatinous metamorphosis of the pelvic bone marrow with possible minor bone marrow insufficiency.

An abnormal EEG pattern compatible with bilateral temporal lobe affection was found. However, cerebral magnetic resonance imaging (MRI) and computerised tomography (CT) did not reveal any brain pathology. The patient showed autoimmunopathy as evidenced by circulating antinuclear autoantibodies, immune complexes, and rheumatoid factor; increased serum IgE; and reactivation picture of Epstein-Barr virus. Autonomic neuropathy was indicated by intermittent hypertension, dissociation between heart frequency and mental agitation, general colon constipation, and abnormal reflexes. Secondary hypogonadism was manifest by an absent libido, chronic secondary amenorrhoea, hypoplasia of the uterus and the mammary glands, and very low levels of basal and stimulated gonadotrophins. She also had disturbed circadian rhythm with a phase advance for cortisol and melatonin secretion.

Other tests detected increased urinary CRF-excretion with discrepant CRF and cortisol levels; increased serum, urine and CSF L-aspartic acid; decreased urinary and CSF L-GABA; decreased CSF HVA, MHPG and 5-HIAA; and decreased blood 5-HT measured while the patient was taking clomipramine. General hypoanalgesia was suggested by lack of response to dental treatment. She had reduced visuospatial brain function and possibly memory function, a somewhat prolonged bleeding time, and increased levels of zinc in scalp hair.

Cytogenic studies

On tests, 28% hyperdiploidy (more than the diploid numbers of 46 chromosomes) was seen in the patient's lymphocytes cultured in normal control plasma as against 17% for control lymphocytes in control plasma, 19% for the patient's lymphocytes in her own plasma and 8% for normal lymphocytes in the patient's plasma. The patient's bone marrow cells showed a 26% hyperdiploidy compared with 0.6% for bone marrow cells of controls (see Table 1).

Dialysed plasma fractions of < 12 kD and to lesser extent > 3.5 kD caused an increased frequency of chromosome fragments and structurally aberrant so-called marker chromosomes in cultured lymphocytes from normal controls (see Table 2).

In a separate study, the patient's lymphocytes were cultured in phytohaemagglutinin (PHA) according to the method of Högstedt (1984) and 13 micronuclei were found per 1000 lymphocytes compared to 3–5 per 1000 for an extensive control population.

Discussion

The polydiploidy (hyperdiploidy) seen in the patient's lymphocytes cultured in normal plasma and the polydiploidy in the patient's bone marrow cells are highly abnormal. The source of this hyperdiploidy is unknown, but it could be the result of aberrant gene expression and resultant metabolic dysfunction. Since it occurs in both lymphocytes and bone marrow cells, it could be a generalised cellular defect which may occur in neurons as well, and may indicate a generalised mitotic instability. Microtubules play a critical role in maintaining cellular architecture and in directing chromosomal alignment and movement during mitosis. Abnormalities in the mitotic process or in the structure or assembly of the alpha-beta-tubulin subunits, which make up the microtubules, could play a role in such intrinsic hyperdiploidy. However, cultured fibroblasts did not show hyperdiploidy. This could indicate that other factors, perhaps in plasma, might be involved. Supporting this, fractions of patient's plasma with material of an apparent molecular weight between 3.5 kD and 12 kD increased the frequency of chromosome fragments and structurally aberrant 'marker chromosomes' in cultured control lymphocytes. This resembles the chromosome damaging factor reported by Emerit (1982) of molecular weight 1–10 kD. Several extrinsic agents also can disrupt spindles (Dellarco *et al*, 1985) as can changes in SH and ATP levels, oxidative damage to membranes and impaired control of cytoplasmic Ca^{2+} levels (Hoffmann, 1985). Some may also cause chromosome breakage. The 3–5-fold increase in the number of micronuclei in the lymphocytes further supports a constitutional abnormality in the patient.

The disturbances in blood-pressure regulation, serum and urine osmolality, and urine production probably merely reflect known medication effects on renal function or autonomous dysfunction. Long-term starvation, as well as anorexia nervosa,

can produce extensive bone marrow gelatinous metamorphosis into a 'thick skull' like that found in this patient (Reeder & Felson, 1975). This bone marrow pathology caused only slight leucopenia and thrombocytopenia.

Raynaud phenomenon, several circulating autoantibodies and a reactivation pattern of Epstein-Barr virus in her serum are indicative of autoimmune processes. Their significance in relation to her psychopathology is unclear. The significance of the elevation in CSF of the excitatory amino acid L-aspartate and the reductions in the inhibitory transmitter GABA, and the monoamine metabolites, HVA, MHPG, and 5-HIAA, are also unclear. Whether the abnormalities detected in this study reflect the cause or consequences of the patient's affliction remains to be determined.

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