

Late-Onset Obsessive-Compulsive Disorder Without Evidence of Focal Cerebral Lesions: A Case Report

SIR: Obsessive-compulsive disorder (OCD) belongs to a rapidly evolving field of psychopathology that goes beyond classical nosological conceptions to meet a broad spectrum of disorders concerning impulse control as a result of structural or biochemical neuronal modifications. Such disorders appear in conditions as Tourette's Syndrome, autism, body dysmorphic disorder, pathological gambling, trichotillomania, hypochondriasis, etc.¹ The concept of spectrum is justified by similarities in symptomatology, prognosis, psychiatric comorbidity, family history, neurobiological overlaps and response to SSRI's.²

OCD is a disabling disease with onset usually in adolescence and early adulthood. According to Weissman et al, the symptoms appear before age 25 in about 2/3 of affected persons,³ and Rasmussen et al state that only in 15% of patients do symptoms begin after age 35.⁴ In late-onset OCD, especially in cases with onset after age 40, Koran stresses that the possibility of an underlying medical condition should be investigated.⁵

Cerebral areas, lesions of which have been related to the appearance of OCD, are the frontal lobe and basal ganglia. The same areas have been implicated in the neuropathology of "idiopathic" OCD⁶; the first such proof came with the work of Lewis Baxter, who demonstrated in

1987 with the use of radioactively labeled glucose that patients suffering from OCD present hyperactivity in the orbitofrontal areas and the caudate nuclei.⁷

In this report, we describe the rare case of a patient with late-onset OCD without any specific underlying cerebral lesions.

Case report:

Mr. L., a 68-year-old married white man, presented himself at the Center of Mental Health Services with obsessive-compulsive symptoms that had appeared two years before. He had then visited a psychiatrist, but had not complied with the prescribed treatment. His symptoms, whose pathological nature he was fully conscious of, consisted of excessive worries of infection. For fear of contamination, he would avoid handshakes; he found it difficult to touch money, he would wash his hands over 30 times a day, he would not touch furniture or door-knobs, and he would meticulously disinfect his clothes. His Yale-Brown OC Scale (Y-BOCS) score was 27 (maximal score 40—for the diagnosis of OCD a score of more than 16 is required). Head scans with computed tomography (CT) and magnetic resonance imaging (MRI) did not reveal any abnormalities. Mr. L. was started on a treatment with paroxetine, whose dose was gradually raised to 40 mg/day. His symptoms resolved after 3 weeks of treatment. Ten months later, Mr. L. continues his treatment and remains asymptomatic.

Comment:

OCD usually occurs in the second and third decade of life. The participation of frontal lobe and basal

ganglia is well known in this disorder, but focal cerebral lesions are usually not found except in the late-onset forms. Although such cases are uncommon, two reports have recently been published concerning the development of OCD after the age of 65, where, however, the majority of cases concerned women.^{6,8} According to a recent epidemiological study by Nestadt et al,⁹ the incidence of OCD is bimodal in men and women, both peaks occurring later in women; the second peak concerns the age spectrum between 30–44 years in men, whereas in women it appears after the age of 65.

The uniqueness of the presented case consists in the fact that it concerns a late-onset, after the age of 65, occurrence of OCD in a man; moreover, no signs of underlying cerebral pathology could be detected, as it usually is the case in late-onset OCD. Interestingly, from the 10 cases described by Weiss et al⁶ and Chacko et al,⁸ only one patient did not show evidence of specific cerebral abnormalities. Our patient's response to medication was excellent, something rather unusual in the "late" forms of OCD.

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Frontotemporal Dementia Presenting with Pathological Gambling

SIR: Pathological gambling (PG) is an impulse control disorder, characterized by a failure to resist the impulse to gamble at the risk of severe personal, family, or vocational consequences.¹ Similarities in decision-making behavior between PG patients and patients with prefrontal cortex lesions have recently sug-

gested a possible implication of these areas in the pathophysiology of gambling.²

Frontotemporal dementia (FTD), is a progressive dementing condition characterized by selective degeneration of the frontal and anterior temporal lobes that causes a profound alteration in character and social conduct, in the context of relative preservation of perception, spatial skills, praxis, and memory.³

Here, we present a patient with FTD whose first symptom was PG. This association has apparently never been reported.

The patient is a 49-year-old male that had an unremarkable medical history since June 1999 when he started gambling with bingo and national lotto. Although gambling left him with significant debts and serious marital discord, he could not stop. Months later, familiars noted a progressive decline in his social conduct, disinhibition, and distractibility, while his PG slowly came to an end. In January 2001, the patient was referred to our Clinic. The neurological examination was unremarkable, except for bilateral grasp reflex. Neuropsychological testing showed a significant impairment on frontal lobe tests, and brain magnetic resonance imaging (MRI) showed predominant frontal and temporal atrophy. A diagnosis of FTD was then made, according to the current diagnostic criteria.³ Over the following months, behavioral changes progressively worsened toward severe frontal lobe dysfunction, with perseveration, echolalia, and poor emotional and cognitive awareness.

In the overactive disinhibited subtype of FTD, as in the case reported here, patients are disinhibited, fatuous, socially inappropriate, and lacking in concern, and pathological changes are relatively confined to orbitofrontal (OFC) and temporal neocortex.³ Interestingly,

it has been recently shown that the OFC is implicated in decision-making processes and emotional-related learning and is involved in the representation of abstract rewards and punishments, such as receiving or losing money,⁴ a specific task that is disrupted in PG.

In our patient, the gambling behavior displayed in the initial phase of the disease was maladaptive, fulfilled the DSM-IV criteria, and was not referable to a coexisting manic state or substance-abuse.¹ Furthermore, in the absence of a previous history of psychiatric disorders or gambling attitudes, it seemed related to the underlying degeneration of the frontal and temporal lobes, characteristic of the FTD.

This patient, then, with coexisting PG and FTD, lends additional support to the suggestion that an abnormal functioning of the OFC might be implicated in the pathophysiology of gambling behavior.²

Many dementing patients lose money control during the course of their disease, but PG has not been recorded as a prominent early feature in previous reports of FTD.³ This disorder, then, could be considered in the differential diagnosis of a new-onset gambling behavior in adults if PG is accompanied by changes of personality and other, more “typical” features of FTD.

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Clozapine-Induced Neuroleptic Malignant Syndrome and Subdural Hematoma

SIR: Neuroleptic malignant syndrome (NMS) is a serious and potentially fatal adverse effect of antipsychotic drugs. Traditionally, NMS is said to occur infrequently with atypical antipsychotics, but increasing reports of atypical antipsychotic-associated NMS calls for further exploration of risk factors for NMS with these medications.¹ One such risk factor is the presence of an underlying brain disorder, which predisposes a patient exposed to conventional antipsychotics for NMS.² A case of clozapine-induced NMS in a patient with subdural hematoma is presented and the possible pathophysiological mechanism is discussed.

Case Report

Mr. A., a 52-year-old male with long-standing bipolar disorder, was admitted with exacerbation of affective and psychotic symptoms following his father's demise. For the past 10 years, he had been stable on 400 mg/day of clozapine. There was no history of drug or alcohol use and he was on nifedipine (20 mg/day) for hypertension. Mr. A. had three prior episodes of NMS secondary to chlorpromazine, lox-

apine and lithium, respectively. During the current admission, he was agitated and had to be restrained as he kept banging his body against the wall, a behavior which had been noticed for few days prior to admission. On day 1 of admission, clozapine was increased to 500 mg/day. On day 4, the patient was found to have altered sensorium, with moderate rigidity, fever (101.7°F), and urinary retention. Other vital signs were stable. Laboratory investigations revealed leucocytosis ($17 \times 10^9/L$; normal range, 4.5 to 11.0), CPK 4883 IU/L (normal range, 0–200), ALT 149 IU/L (normal < 40) and AST 192 IU/L (normal < 40). Urine analysis was positive for proteins (100mg/dl; normal 0). Electrolytes, creatinine and blood urea nitrogen were normal. EEG showed a generalized background slowing while MRI of the brain revealed a subacute bilateral frontal hematoma. Clozapine was immediately stopped and patient was treated symptomatically and with intravenous fluids. On day 5, the CPK peaked at 18,000 IU/L and then began to drop, reaching 175 IU/L on day 9, with resolution of altered mental status, fever and rigidity. A head CT scan before discharge showed a resolving subdural hematoma. The patient was subsequently treated with lorazepam and valproate.

Comment

This case provides an insight into the neurobiological basis of NMS in patients with an underlying brain injury. This patient may have sustained a subdural hematoma secondary to the self-injurious behavior. The notable feature of this presentation was that the patient developed NMS with clozapine after being stable on it for 10 years. Although it cannot be denied that concurrent agitation and the previ-

ous history of NMS may have contributed to the index episode of NMS, the incidental finding of subdural hematoma raises the specter of brain injury predisposing to NMS. There are reports of underlying cerebral conditions being a risk factor for NMS, but these are mostly limited to patients with delirium tremens, post-operative delirium, dementia of Alzheimer's type, and mental retardation.^{2,3} Furthermore, there are anecdotal reports of NMS occurring in patients with traumatic brain injury treated with conventional antipsychotics but none with atypical antipsychotics.⁴ However, these reports do not expound on any new mechanisms of central nervous system disorders predisposing to NMS.

Reduced dopaminergic transmission has been shown in patients with traumatic brain injury.⁴ In addition, an animal study besides demonstrating a decreased utilization of dopamine in brain following cerebral concussion also showed an increased utilization of serotonin.⁵ Dopamine hypoactivity is a putative hypothesis of NMS, but recent literature also emphasizes serotonergic, particularly 5-HT_{1A} hyperactivity, as contributing to NMS.⁶ Brain injury with its resultant increase in serotonergic transmission and the 5-HT_{2A} blockade by clozapine favors a selective stimulation of 5-HT_{1A} receptors. Thus traumatic brain injury along with concomitant clozapine may have predisposed this patient for NMS. Hence caution is advised while treating brain-injured patients with atypical antipsychotics, especially in the presence of other risk factors for NMS. Finally, the serotonergic hypothesis of NMS deserves further attention considering reports of selective serotonin reuptake inhibitors precipitating NMS.⁷

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Delirium Induced by Abrupt Discontinuation of Paroxetine

Case Report

SIR: The patient was a 73-year-old woman who developed major depression triggered by domestic stress in June 2002. She was prescribed 40 mg of paroxetine and 0.8 mg of alprazolam at bedtime and 3 mg of etizolam during the day. Full remission resulted, and treatment was maintained.

The patient remained well until August 2002, when she was admitted to the urology department of a hospital as a kidney donor for her daughter. She received a last dosage of medication at bedtime on the

day before surgery. At 07:00 the following day, diazepam (2 mg) and ranitidine hydrochloride (150 mg) were administered preoperatively. Left-side donor nephrectomy was performed following intravenous injection of thiopental (200 mg) at 10:00 and inhalation with sevoflurane for maintenance of general anesthesia. The operation was completed without complications at 14:00. By 14:30, the patient had completely regained consciousness. Post-operative laboratory data revealed no abnormalities. However, symptoms of thirst and dizziness were suddenly reported from 16:00. Thereafter, disorderly behavior gradually developed. At 21:20, a urologist administered etizolam (1 mg) and alprazolam (0.8 mg), but the patient remained agitated and complained of visual hallucinations such as insects. Since psychotic symptoms persisted despite intravenous injection of haloperidol (5 mg) at 22:25, diazepam (5 mg) at 23:40, and hydroxyzine hydrochloride (50 mg) at 01:57 the following day, the urologist referred the patient to a psychiatrist (the author) at 10:00 the next morning. Although visual hallucinations had disappeared, a diagnosis of delirium was made since the patient was assessed to be not fully oriented and was unable to follow verbal commands (Japan Coma Scale score = 1-3). Tiapride hydrochloride (75 mg) during the day and chlorpromazine (15 mg) at bedtime were prescribed and the patient slept well. Psychotic manifestations had resolved completely by 10:30 on postoperative day 2.

Comments

We attribute delirium in this case to the abrupt withdrawal of paroxetine, because: 1) the patient had been taking a relatively high dose of paroxetine for a prolonged period; 2) delirium appeared soon after cessation of paroxetine; 3) delirium

developed despite absence of intraoperative complications; 4) delirium was preceded by thirst and dizziness, which are common symptoms of SSRI withdrawal;¹ 5) no drugs known to interact with paroxetine² were administered intraoperatively; and 6) full recovery from delirium occurred within a short period. Another possible candidate for withdrawal delirium in this case was benzodiazepine. However, as psychotic manifestations were exacerbated despite administration of benzodiazepine before surgery and in the period when delirium initially appeared, discontinuation of benzodiazepine seems unlikely to have caused the delirium.

Paroxetine is reportedly more likely to induce withdrawal symptoms than other SSRIs, due to the following pharmacokinetics^{3,4,5}: (1) short half-life; (2) absence of active metabolites; and (3) non-linear kinetics. Physicians should pay close attention to delirium as well as other symptoms of SSRIs, particularly in cases in whom high-dose paroxetine has been maintained for long periods.

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Frontotemporal Arachnoid Cyst Connected to Relapsing Stupor

Case Report

SIR: A 45-year-old married woman was admitted to our hospital for the first time in January 1983. At first, she was depressed, hypo mimic, and she didn't speak. Since she had symptoms of major depression, we started the therapy with maprotiline and thioridazine. Her condition deteriorated, she began refusing food and liquid. We started with an i.v. treatment with maprotiline, but her condition still worsened along with the EPS (tremor, rigor). After that, she had three ECTs. She became febrile and dehydrated. There were no signs of improvement. We assumed that stupor was organic in origin, so we referred her to the CT scan, which revealed an arachnoid cyst 5cm by 7cm in the region of the left frontotemporal lobe. She was sent to Neurosurgery Clinic of Ljubljana, where the patient underwent an operation. Her condition improved immediately without any medication.

The second admission was in 1986. She was in stupor again. The CT scan revealed arachnoid cyst in the same region as the first time. The cyst sized 3cm in diameter. The

neurosurgeon decided for non-surgical procedure, since she already had an aqueduct by-pass done. Psychiatric therapy proceeded with the selection of sulpiride, which she was taking orally.

In the following years, the same clinical picture appeared whenever she faced any minor stress life events (her sons wedding, conflicts with neighbors and similar). The successful therapy proved to be sulpiride, carbamazepine and lorazepam. After 1995, she became very religious, but no delusions were noticed.

She was last admitted to our hospital in March of 2001. She had been denying food intake and liquids three days prior to admission; she was depressed and had auditory hallucinations and paranoid delusions. Her medication consisted of sulpiride, carbamazepine, lorazepam, tianeptine and finally olanzapine and doxepine. The neurological examination revealed no specific pathology. The CT scan showed again large frontotemporal cyst with the tip of catheter seen along with enlarged ventricles in close vicinity of limbic structures. She was to go to the neurosurgeon, but abruptly, although CPR was performed, died because of massive pulmonary embolism.

In the past 20 years, we accidentally discovered 4 patients with arachnoid cysts. The literature describes catatonic symptoms in 14-year old boy with anorexia nervosa¹ and mental disturbances are connected to arachnoid cysts in children.² Case studies reported on differential diagnosis of schizophrenia in patients with bilateral temporal cysts.^{3,4,5}

We treated our patient for twenty years. There are no reports in available medical literature of such long treatment. We would like to emphasize the connection between cyst and symptoms, which, in our case,

were always depression, which gradually developed to stupor.

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Parity, Number of Pregnancies, and the Age of Onset of Alzheimer's Disease

SIR: Estrogen deprivation has been implicated as a risk factor in Alzheimer's disease (AD), as some epidemiological data suggest that hormone replacement therapy (HRT) can modulate the risk of the disease. However, neither endogenous sex hormone levels in postmenopausal women¹ nor the lifetime exposure to estrogens measured by the length of reproductive period² represents irrefutable factors modulating the risk or the course of cognitive decline in AD. The issue of

the possible connection of endogenous estrogens and age-related cognitive decline has been raised again recently in the report of McLay et al³ who observed that nulliparity and late menopause (both understood as surrogate measures of endogenous estrogens exposure) resulted in decreased cognitive decline in non-demented women. The association between late menopause and age at onset of AD (which might represent a marker of the rate of cognitive decline) has been shown by several groups, including ours.⁴ In the cohort of 65 sporadic AD cases in women we were also able to show the significant negative relationship between number of pregnancies and age at onset of AD: women with more pregnancies had younger age-at-onset (Pearson's $R = -0.65$, $p < 0.01$). In the regression model including age, age at menopause, education and smoking behavior, number of pregnancies was an independent factor (rather surprisingly even stronger than the age at menopause alone) and with each pregnancy the age of onset of AD was reduced by almost three years.

The relationship between parity (or number of pregnancies) and both cognitive decline rate in non-

demented women³ and the age of onset of AD⁴ is difficult to interpret. One possible explanation is linked to estrogens solely: estrogen levels are very high during pregnancy and drop acutely thereafter with decreased levels maintained for approximately one year; furthermore, parity influences estrogen levels later in life. Both observations are in agreement with higher lifetime exposure to estrogens in nulliparous women. Alternatively, one can reason that progestins (which levels are also elevated in pregnancy) might play an independent role and even outweigh the benefits of estrogens, that might in part explain the recently reported failure of HRT in preventing AD or mild cognitive impairment⁵ and puts forward a question of the conditions (mainly safety issues) of estrogens alone replacement as an AD preventing strategy. Another unsolved question is the role of different progestins in the development of the cognitive decline (e.g., 17OH-progesterone and progesterone from different sources during pregnancy, like luteal corpora or placenta) and, finally, the use of the diverse progestins in the HRT and their potential role in the dementia prevention or treatment strategies.

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CORRECTION:

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Angela Scicutella, M.D., Ph.D. should have been included in the list of reviewers on page 471.