Risperidone-induced acromegaly: a case report

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Abstract: Today, considering their adverse side effects, the first-generation antipsychotics have been replaced by the new-generation antipsychotics (also known as second-generation antipsychotic agents). The superiority of new-generation antipsychotics compared with first-generation antipsychotic agents in terms of side effects, especially movement disorders, are acknowledged by clinicians. But in recent years during the use of second-generation antipsychotic agents, endocrine side effects have been noteworthy. In our study with a diagnosis of paranoid schizophrenia treated with risperidone for 14 years and operated with the diagnosis of pituitary macroadenoma, a 32-year-old female patient is presented in the light of the literature examining the framework of the history of disease.

Keywords: acromegaly, endocrine side effects, risperidone

Introduction

Despite pharmacological advances, the treatment of schizophrenia remains a challenge, and suboptimal outcomes are still all-too frequent. Although treatment goals of response, remission, and recovery have been defined more uniformly, a good 'effectiveness' measure mapping onto functional outcomes is still lacking. Whereas the acute response to appropriately dosed first-generation antipsychotics may not differ much from second-generation antipsychotics, the advantages of lower rates of extrapyramidal side effects, tardive dyskinesia and, possibly, relapse may favor second-generation antipsychotics. However, when considering individual adverse effect profiles, the differentiation into first- and second-generation antipsychotics as unified classes cannot be upheld, and a more differentiated view and treatment selection is required [Kane and Correll, 2010]. Therapy is usually started to keep the patient out of hospital and, in some cases, the side effects of the drugs have altered the patient's life significantly. The frequency of the occurrence of movement disorder has especially decreased with the use of second-generation antipsychotics. The second-generation antipsychotics are generally effective in treating the positive as well as negative symptoms of schizophrenia, influencing the serotonergic and dopaminergic system receptors [Tajima *et al.* 2009; Blanc *et al.* 2010].

The mechanisms of many side effects of the antipsychotics are described as receptor blockage. For example, the extrapyramidal symptoms (EPSs) similar to Parkinson's disease appear to be dependent on decreased dopamine activity through dopamine receptor blockage in the nigrostriatal pathway; however, dopamine blockage in the hypothalamic and pituitary systems has resulted in hyperprolactinemia [Pramyothin and Khaodhiar, 2010]. Most second-generation antipsychotics do not cause a sustained elevation in prolactin levels, whereas antipsychotic-induced hyperprolactinemia is almost universal with first-generation antipsychotics agents. The reason for the use of the second-generation antipsychotics has been reduced EPSs and also endocrinological side effects, due to their influence on the positive and negative symptoms of schizophrenia [Newcomer, 2005; Coccurello and Moles, 2010; Kurt *et al.* 2008]. A typical drug is risperidone, a derivative of benzoxazole that shows affinity for 5-HT_{2A} serotonin receptors (5-HT2A) and for D_2-dopamine receptors (D2), together with H_1-histamine (H1) receptor, alpha -1 and alpha-2 adrenergic receptor blockade. Risperidone is unique among most other 'atypicals' in that it has high affinity for the D2 receptor. The affinity of risperidone for 5-HT2A is 10–20 times more than for the D2 receptor. The most common side effects are EPSs, weight

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gain, hyperprolactinemia, orthostatic hypotension and somnolence [Komossa *et al.* 2011]. Endocrinological system side effects are not limited to the increase in prolactin and the impaired glucose tolerance test and diabetes mellitus have also been recorded [Kim *et al.* 2002]. Many antipsychotics are known to cause hyperprolactinemia, which may lead to hypogonadism-induced osteoporosis, galactorrhoea, gynaecomastia (male breast development), irregular menstruation and sexual dysfunction. Risperidone is one of the second-generation antipsychotics most likely to induce hyperprolactinemia, whereas this is infrequently and only transiently associated with other second-generation antipsychotics. Women are more sensitive than men to these effects and risperidone-induced hyperprolactinemia is at least at a similar level to that found with the first-generation antipsychotics [Halbreich *et al.* 2003].

Acromegaly, a growth hormone (GH)-secreting pituitary adenoma, is due to chronic GH hypersecretion [Melmed *et al.* 2005]. At diagnosis, about 75% of patients have macroadenomas. The annual incidence is about 3 or 4 cases per 1,000,000, which is probably an underestimate. The mean age at diagnosis is about 45 years. Rarely, multiple endocrine neoplasia type -1 (MEN-1), McCune Albright syndrome, is seen with the genetic syndromes such as familial acromegaly and Carney complex. Acromegaly diagnosis is based on clinical and biochemical results. When acromegaly is suspected, the measurement of serum insulin-like growth factor-1 (IGF-1) value should be the first step. IGF-1 levels should be evaluated taking age and gender into account. Acromegalic patients in general complain of coarsening of the face, growth in the extremities, headache, fatigue, excessive sweating, and gonadal dysfunction [Lopes, 2010]. High GH and IGF-1 levels lead a clinical table containing arthritis, facial changes, prognathism, and glucose intolerance. If untreated, mortality associated with cardiovascular, cerebrovascular and pulmonary dysfunction increases and life expectancy reduces by 30% [Melmed, 2009].

Our study presents a 32-year-old female patient with a diagnosis of paranoid schizophrenia, treated with risperidone for 14 years and operated on with the diagnosis of pituitary macroadenoma, in the light of the literature examining in the framework of the history disease.

Case report

Mrs NR, 32 years old, high school graduate, single, a housewife was born in a district of Rize in Turkey and her family still lives in the same district. She was brought involuntarily to our hospital by her family with the complaints of paranoia, introversion, self-laughing, and refused to speak, eat, or leave her house. She also rejected other people's company and preferred to stay on her own. She could not sleep.

History

Fifteen years previously the patient started complaining of absent-mindedness, social withdrawal, malaise, away from people, suspicion and crying. She left the house in the morning and was brought home by her relatives at night. She was initially taken to a neurology specialist. In her neurological examination, electroencephalography (EEG) and cranial computed tomography (CT) scans, no pathologic findings were detected. At that time, the patient's family could not explain behaviors such as hiding her sister's clothes and talking to herself, laughing by herself, and raising her eyes from time to time. She was afraid of the guests coming home or some passing cars on the road and some signboards in the street and complained of ringing sounds in her ears. The patient was referred to a psychiatric clinic of a training hospital by the neurology specialist and was admitted for psychiatric hospital tests and she was started on the treatment of risperidone 6 mg/day. After 2 months treatment as an inpatient, the patient's complaints were reduced. She then applied to the hospital's psychiatric clinic after discharge for a while in order to be controlled at regular intervals and continued to take the treatment of risperidone 2 mg/day. The patient continued to use the drugs without resorting to a doctor for 5 years, experiencing some problems after 3 years such as swelling of her feet and hands, amenorrhea, weight gain, coarsening facial lines, and changing voice tone, as confirmed by her family. She was taken to the psychiatric clinic of the our hospital and was referred to the neurosurgery clinic after 28 × 28 × 32 mm3 macroadenoma invading the right cavernous sinus and obliterating sphenoid sinus in pituitary gland was diagnosed in both the sagittal and coronal planes, after magnetic resonance imaging (MRI) was carried out. The patient's pituitary macroadenoma was hypersecreting GH, measured at 31.7 ng/ml and the IGF-1 value was 1202 ng/ml

and was surgically excised in the neurosurgery department of a different education hospital. The patient who was started on cabergoline 0.5 mg treatment two times per week after discharge from the hospital's neurosurgery clinic had high GH levels and was admitted to the endocrinology service of the same hospital for further evaluation and treatment. Here MRI of the pituitary gland showed that the macroadenoma was almost the same size as when the preoperative lesion was detected in the pituitary log. At that hospital, after the required brain surgery consultation, a surgical approach was not considered necessary, and subcutaneous oktreotit treatment was started. She was taken to our psychiatric outpatient clinic for the second time after the operation and medical intervention.

Case history

Mrs NR, of a normal birth, was given birth to at home as the third child of a family with four children. No problem or retardation was identified in growth and development. She completed her primary, secondary and high school education in the same district. She was such a quiet and introverted child that she had few school friends at school and her school performance was at a medium level. Her parents are alive and healthy, cousins of each other and married 39 years ago after family arrangement. The mother is a primary school graduate, a housewife and the father left secondary school and for up to 7 years worked in his own workplace but due to bankruptcy, had to close the workplace. In this period the family lived through major economic problems. Mrs NR's two older brothers and younger sister are married and live separately from her. She was very upset especially when her sister who she got along well with left home because of marriage. The patient has worked in her father's workplace for a while and attended driver's license and computer classes, but did not complete the courses. She has smoked one pack of cigarettes a day for 16 years and increased this amount during periods of distress. In particular, in recent years she has preferred to sleep during the day, sit in her room until late at night and not to go away from home. A known neurological, psychiatric disease has not been identified in the family.

Physical examination

The patient whose facial lines were coarsening had a dysphonic tone of voice. In visual field examination, bilateral heteronymous hemianopia was available. Acral growth was detected in the extremities.

Pituitary MRI

A pituitary macroadenoma, 28 × 28 × 32 mm3 in size, extending suprasellar region in sella, on T1 and T2 images, showing homogeneous contrast with gray matter relatively isointense was detected. The pituitary gland parenchyma had pushed to the left lateral and the pituitary stalk moved to the left. There was pronounced mass lesion extending to the right cavernous sinus and surrounding the right internal carotid artery (ICA) 360°. This mass lesion extended from the network posterolateral to the neighborhood of temporal lobe medial. The suprasellar cistern was contracted. The sphenoid sinus was completely obliterated. Bilateral temporal scotoma was detected as a result of the eye disease consultation and it was observed that left ventricular diastolic dysfunction had developed in cardiological tests. Ejection fraction was measured as 65%.

Laboratory measurements

Prolactin: 120 ng/ml; GH: 31.7 ng/ml; IGF-1: 1202 ng/ml; glucose: 134 mg/dl; Low-density lipoprotein cholesterol: 134 mg/dl.

Psychiatric evaluation

At her psychiatric appointment, the female patient, who looked older than her years, looked well groomed and behaved with respect. She was reluctant to speak. In her appearance, growth especially on the face and hands was remarkable. She was conscious and her orientation was complete. In her speech, dysphonic (tone of voice is rude) and use of regional accent was present with purpose-built short sentences. Her affection was superficial. Auditory hallucinations, decreases in thinking process and speed, no break in and no block were observed. It was noted that her thought content is impoverished and she has apparent reference persecution delusions.

Findings

Risperidone treatment was stopped after the above observations. Having experienced increases in psychiatric symptoms, the patient's treatment was changed to quetiapine 400 mg/day. Currently,

the patient's psychiatric treatment and controls are ongoing and her complaints have partially decreased.

Discussion

As a consequence of their prolactin-raising properties, some antipsychotics may be associated with an increased risk of pituitary tumor development [Montejo, 2008]. Investigators screened the US Food and Drug Administration (FDA) Adverse Event Reporting System Database (a voluntary reporting system with a database of 2.5 million reported adverse events) to determine the relative frequency and association between seven antipsychotic medications (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and haloperidol) and reports of pituitary tumors, as well as hyperprolactinaemia and galactorrhea [Szarfman *et al.* 2006]. Our study reported pituitary macroadenoma occurring during the use of risperidone in 14 years and recurring as a result of continued use of risperidone after excision, and the case of acromegaly. Risperidone demonstrated the highest adjusted reporting ratio (i.e. the strongest association between the drug and an adverse event) for pituitary tumors followed by haloperidol, ziprasidone and olanzapine. The incidence of reports of hyperprolactinaemia and galactorrhoea were also higher with risperidone than with other antipsychotics. In the literature, hyperprolactinemia, one of the endocrinological side effects due to antipsychotics, has been frequently observed; however, pituitary macroadenoma has not been reported. Pituitary adenomas constitute 10–20% of all intracranial neoplasm [Erer *et al.* 2008]. The development of pituitary adenoma is considered to be multifactorial. It is thought that a somatic point mutation arises initially in one cell and the event progresses with secondary mutations. Environmental factors, growth factors, hormones and changes in receptors influence the behavior of biological changes in tumors [Shahlaie *et al.* 2010]. Pituitary adenomas result in significant morbidity due to local pressure effects and hormone hypersecretions. Treatment requires the work of a team of brain surgeons, endocrinologists and radiation oncologists [Debono and Newell-Price, 2010]. The most common cause of acromegaly is pituitary adenomas synthesizing GH and it is a known risk factor for cardiovascular mortality. When GH secretion cannot be controlled in these patients, the metabolic changes result in mortality and/or morbidity. Compared with the general population, acromegalic patients have 2.4- to 4.8-fold increased mortality rate [Holdaway *et al.* 2004; Kauppinen-Makelin *et al.* 2005]. Elevated prolactin levels are seen in ~30% of patients [Komossa *et al.* 2011]. Although studies cannot establish the absence or presence of a causal relationship between second-generation antipsychotic agents treatment generally (and risperidone treatment specifically), and pituitary adenomas, it is important to recognize that pituitary adenomas of clinical relevance may still occur in patients receiving antipsychotic medication, and that patients with symptoms suggesting pituitary adenomas should receive full appropriate evaluation. As with other second-generation antipsychotics, endocrinological side effects were identified and pituitary macroadenoma cases increasing with growth hormone due to risperidone treatment have been reported for the first time, which gives importance to our case study. According to Gianfrancesco and colleagues (as reported in the pharmacovigilance study by Szarfman et al. [2006]), compared with other antipsychotics, risperidone-treated patients were found to have a higher risk of the occurrence of pituitary tumors [Gianfrancesco et al. 2009]. This suggests that, when a high level of prolactin is detected in patients treated with risperidone, it is worth doing pituitary tumor research using brain imaging studies, because these tumors are usually small, benign and remain endocrinologically silent [Lopes, 2010]. In a study of Kurt and colleagues, it was shown that even the use of low-dose risperidone causes more prolactin increase compared with haloperidol [Kurt et al. 2008]. Risperidone-treated patients are more likely to undergo prolactin assessment regardless of prior prolactin-related adverse events, and more likely to undergo MRI in association with hyperprolactinemia. Thus, a predisposition for more evaluations in risperidone-treated patients may contribute to disproportionate identification and reporting of prevalent pituitary adenoma [Gianfrancesco et al. 2009].

Atypical antipsychotic drugs are now often preferred, particularly in the treatment of patients with psychotic disorders. It is clear that these drugs, which, in comparison with typical antipsychotic agents, can be very well tolerated, should be used with great care during long-term use, especially in terms of endocrine side effects.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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