Curious Cases: Acromegaly and Schizophrenia: An Incidental Association?

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Objective: Acromegaly associated to schizophrenia was first reported ~60 years ago, and so far, it is unclear whether this association is causal or not. Our aim was to report new cases with both clinical entities and to discuss the potential pathophysiological mechanisms of this association. Methods: Three new cases and data from literature are reviewed. Results: We report 2 males and 1 female diagnosed with schizophrenia and treated for several years with antipsychotics who developed acromegaly due to a growth hormone (GH)-secreting pituitary macroadenoma. In all cases, the diagnosis of schizophrenia preceded acromegaly with mean disease duration of ~12 years. Antipsychotic therapy was different in every patient. Two patients underwent transsphenoidal surgery. Histopathological study showed mixed GH- and prolactin-secreting adenoma in 1 patient and pure GH-secreting adenoma in the other patient. Several pathophysiological mechanisms related to alterations in dopaminergic neurotransmission due to psychiatric disease itself or its pharmacological treatment are proposed and discussed as likely linkage between schizophrenia and acromegaly. Conclusion: These case reports suggest that schizophrenia and/or its antipsychotic therapy in the long term might be in relation with the development of GH-secreting pituitary adenomas.

Key words: acromegaly/schizophrenia/pituitary adenoma/growth hormone/dopamine

Introduction

Schizophrenia is a severe and chronic mental psychiatric disorder characterized by hallucinations or delusions, disorganized speech, flat affect or poverty of speech, and impairments in cognition including attention, memory, and executive functions. The biological basis of schizophrenia involves a combination of genetic and environmental factors. Its diagnosis is associated with demonstrable alterations in brain structure and changes in dopamine (DA) neurotransmission.

Background

DA, a neurotransmitter produced in several areas of the brain, such as the substantia nigra and the ventral tegmental area, activates the 5 known types of DA receptors (DR). In the brain, DA have multiple functions including important roles in behavior and cognition, voluntary movement, motivation, punishment and reward, sleep, mood, attention, working memory, and learning. On the other hand, DA is also a neurohormone released by the hypothalamus whose main function is to inhibit prolactin (PRL) release from the lactotrop cells of the anterior lobe of the pituitary gland. Moreover, DA is a precursor of norepinephrine, which increases and inhibits growth hormone (GH) secretion via α- and β-adrenergic pathways, respectively.

The first clinical case with schizophrenia and acromegaly was reported by Hofmann ~60 years ago. So far, this association has been exceptionally documented. We herein report 3 new acromegalic patients with schizophrenia and discuss the possible relationship between both clinical entities.

Case Reports

Three acromegalic patients (1 woman and 2 men) diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (American Psychiatric Association, 2000) are presented (table 1).

Case 1

A 44-year-old male with a history of chronic human immunodeficiency virus infection (clinical category A2), chronic infection with hepatitis C virus (genotype
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1a), and paranoid schizophrenia of ~20 years of evolution was referred in May 2011 for study of a pituitary mass. He was on therapy with antiretrovirals (abacavir 600 mg/d, lamivudine 300 mg/d, and nevirapine 400 mg/d) and with psychoactive drugs (paliperidone 12 mg/d and amisulpride 400 mg/d). Doses of these drugs remained stable in recent years. His infectious disease specialist had called attention on the physical appearance of his face and hands in the last year. The patient reported headaches, increased acral growth (hands and feet), voice changes, hyperhidrosis, thickening of facial skin, erectile dysfunction, and slightly reduced right temporal visual field. Hormone investigations revealed high levels of GH (67.9 ng/ml [N: 0.05–6.00]), insulin-like growth factor type 1 (IGF-1; 1107 ng/ml [N:101–267]) and PRL (148 ng/ml [N: 2.5–17]) with low serum concentrations of testosterone (210 ng/dl [N: 300–900]). The rest of the pituitary hormone concentrations were normal. Magnetic resonance imaging (MRI) of the pituitary gland revealed a pituitary macroadenoma (22 × 19 × 24 mm) without clear compression on the optical path (figure 1). The patient was operated via transsphenoidal approach, and the pathological study showed a mixed GH- and PRL-secreting pituitary adenoma.

Case 2

A 58-year-old female was referred in 2003 for hormonal study due to clinical suspicion of acromegaly. She had been diagnosed of paranoid schizophrenia many years before and institutionalized since 2002. At that point, she was on therapy with clozapine (600 mg/d) and valproic acid (1100 mg/d). Serum hormone concentrations were as follows: GH 16 ng/ml; IGF-1 704 ng/ml; PRL 24.4 ng/ml; TSH 0.78 mcU/ml; free thyroxine (FT4) 0.8 ng/dl; follicle-stimulating hormone 2.2 mU/ml; luteinizing hormone <1 mU/ml; estradiol 13 pg/ml; and corticotropin 11 pg/ml. MRI revealed a pituitary macroadenoma (13 × 13 × 8 mm) with invasion of the cavernous sinuses. She was diagnosed of acromegaly by a GH-secreting pituitary macroadenoma with involvement of the gonadal and thyroid axes and mild hyperprolactinemia. The patient refused surgical intervention so medical treatment with somatostatin analogs was begun.

Case 3

A 64-year-old male diagnosed of schizophrenia in 2000 and chronically treated with haloperidol (10 mg/d) was referred in July 2002 because of suspicion of acromegaly. Initial hormonal study confirmed the diagnosis (GH 9 ng/dl and IGF-1 831 ng/ml) showing normal serum PRL (18.6 ng/ml) and cortisol (21 mcg/dl) concentrations. Thyroid function tests show subclinical hypothyroidism (TSH 7.27 mcU/ml and FT4 0.79 ng/dl) in relation to the antecedent of a right hemithyroidectomy in May 2002. On MRI, an intrasellar pituitary macroadenoma

<table>
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<th>Table 1. Clinical Features of the Reported Cases</th>
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<td>Male, 64</td>
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Notes: GH, growth hormone; PRL, prolactin; MRI, magnetic resonance imaging; NA, not available.

Stable-dose regimen in the last 3 y.
(12 × 11 mm) was found. The patient underwent surgery in September 2005 by transsphenoidal approach. Pathological investigation revealed a pure GH-secreting pituitary adenoma.

**Considerations**

Schizophrenia is a severe psychiatric disorder that affects ~0.5% of the population, i.e., ~4500–5000 per million\(^9\),\(^{10}\) with an annual incidence of 11–15 per 100 000 person-years.\(^{10,11}\) On the other hand, acromegaly is an uncommon disease that results from excessive secretion of GH, and consequently IGF-1, usually (~90%) due to a GH-secreting pituitary adenoma.\(^12\) Its estimated prevalence is 40–70 persons per million with 3–4 new cases per million per year.\(^{13}\) Epidemiology of acromegaly in Spain does not differ from that reported in other published series (~60 cases per million).\(^{14}\) Therefore, in our country (population of ~47 million people), there must be ~230 000 patients with schizophrenia. Approximately, 14 of them might have concomitant acromegaly. Using the same calculations, there must be ~32 500 patients with schizophrenia and ~2 patients with both diseases in Madrid metropolitan area (~6.5 million general population). Our institutions (Hospital Ramón y Cajal and Hospital 12 de Octubre) are the reference hospitals for a population of about 1 million people. For this population, there must be ~5000 patients with both clinical entities, suggesting an observed prevalence 10 times higher than expected for general population. Therefore, the coexistence of both clinical entities might indicate the presence of a causal connection as it was suggested more than 40 years ago.\(^4\)

Several facts would support this association: (1) in normal subjects, oral administration of L-dopa, the immediate metabolic precursor of DA, stimulates GH release by stimulating hypothalamic DR, and adrenergic blockade with propranolol enhances the GH response to L-dopa;\(^{15}\) (2) dopaminergic mechanisms have been implicated in the pathogenesis of schizophrenia, which shows changes in DA neurotransmission, such as increase in DA synthesis, DA release, and resting-state synaptic DA concentrations; based on these neurochemical findings, therapy with antipsychotic drugs, which block dopamine D2 receptors (DR2), is considered the first-line medication treatment for this disorder;\(^{16}\) (3) this therapy has also been associated to pituitary tumors,\(^{17}\) with a recent report of risperidone-induced acromegaly;\(^8\) (4) DA agonists use such as bromocriptine, even at low doses, has been associated to relapse in treated and previously stable schizophrenic acromegalic patients;\(^{18}\) and (5) DA agonist drugs, in particular cabergoline, inhibit GH secretion normalizing IGF-I levels in about one-third of acromegalic patients.\(^{19}\)

Mental alterations are substantially increased in acromegaly being usually present before the diagnosis of acromegaly. Since its first description by Hofmann in 1953,\(^3\) the association of acromegaly and schizophrenia has been exceptionally reported.\(^3\) Some of these patients were not under DA agonist therapy when developed psychiatric symptoms, but they had been treated with antipsychotic drugs, such as haloperidol,\(^6\) olanzapine,\(^7\) and risperidone\(^8\) before acromegaly diagnosis. We are aware that the number of reported cases so far has been scarce, although it could be related to the low prevalence of both clinical entities, especially of acromegaly.

We can speculate that either chronic changes in DA neurotransmission associated to schizophrenia or long-term psychiatric treatment with DA antagonists might be in relation to the development of GH-secreting pituitary tumors, as it has been reported with prolactinomas in schizophrenic patients treated with risperidone, amisulpride, olanzapine, haloperidol, ziprasidone, and clozapine.\(^{20}\) Indeed, patient #1, who was chronically treated with amisulpride and paliperidone, the major

**Fig. 1.** Magnetic resonance imaging (MRI) coronal (left) and sagittal (right) sections showing a mixed growth hormone- and prolactin-secreting macroadenoma (patient #1) 19 y after schizophrenia diagnosis with a normal initial MRI study of the pituitary.
metabolite of risperidone, developed a mixed GH- and PRL-secreting macroadenoma. On the other hand, in all 3 herein reported patients, the diagnosis of schizophrenia, and therefore, therapy with DA antagonists, preceded in several years the diagnosis of acromegaly.

In conclusion, the association between schizophrenia and acromegaly might not be incidental, and it can be speculated that several pathophysiological mechanisms related to alterations in DA neurotransmission due to psychiatric disease itself or its pharmacological treatment could be in relation with the development of GH-secreting pituitary adenomas. Given the prevalence of schizophrenia, epidemiological studies are suggested to answer this question.

Questions

Is there any relationship between schizophrenia and acromegaly or its therapy? Would it be advisable to perform morphological studies using pituitary MRI over time in schizophrenic patients? What would be the best psychopharmacological treatment for a schizophrenic patient with acromegaly?

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References