CASE REPORT

Cerebral calcifications and schizophreniform disorder

Calcificações cerebrais e transtorno esquizofreniforme

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ABSTRACT

Objectives: Discuss pathophysiological aspects of cerebral calcifications (CC) and highlight its importance related to the occurrence of neuropsychiatric syndromes. **Method:** Single case report. **Result:** Man 52 years old, 20 years after going through a total thyroidectomy, starts showing behavioral disturbance (psychotic syndrome). He was diagnosed as schizophrenic (paranoid subtype) and submitted to outpatient psychiatric treatment. During a psychiatric admission to evaluate his progressive cognitive and motor deterioration, we identified a dementia syndrome and extensive cerebral calcifications, derived from iatrogenic hypoparathyroidism. **Conclusion:** The calcium and phosphorus disturbances, including hypoparathyroidism, are common causes of CC. Its symptoms can imitate psychiatric disorders and produce serious and permanent cognitive sequelae. The exclusion of organicity is mandatory in any psychiatric investigative diagnosis in order to avoid unfavorable outcomes, such as in the present case report.

Keywords
Basal ganglia calcification, organic psychosis, Fahr's disease, dementia, schizophreniform disorder, calcium and phosphorus metabolism disturbances, hypoparathyroidism.

RESUMO

Objetivos: Discutir aspectos fisiopatológicos das calcificações cerebrais (CC) e ressaltar sua importância na ocorrência de síndromes neuropsiquiátricas. **Método:** Relato de caso individual. **Resultado:** Homem 52 anos de idade, 20 anos após tireoidectomia total, iniciou com alteração comportamental (síndrome psicótica), foi diagnosticado como portador de esquizofrenia paranoide e encaminhado para ambulatório de psiquiatria. Durante internação psiquiátrica, para avaliação de importante deterioração cognitivo e motora, foi verificada a vigência de síndrome demencial e extensas CC, secundários a hipoparatiroidismo iatrogênico. **Conclusão:** Os distúrbios do metabolismo do cálcio e do fósforo, incluindo o hipoparatiroidismo, são causas frequentes de CC. Seus sintomas podem mimetizar transtornos psiquiátricos e provocar sequelas cognitivas permanentes. A exclusão de organicidade é mandatória durante toda investigação diagnóstica na psiquiatria, a fim de evitar desfechos desfavoráveis, como no presente relato de caso.

Palavras-chave
Calcificação dos gânglios da base, psicose orgânica, doença de Fahr, demência, transtorno esquizofreniforme, distúrbios do metabolismo do cálcio e fósforo, hipoparatireoidismo.

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INTRODUCTION

Cerebral calcifications (CC) are not uncommon and can occur in several clinical conditions. Historically recognized as Fahr's syndrome, they can vary in presentation from accidental findings to severe neuropsychiatric syndromes[1-4]. Researchers have found that lesions are usually located at the basal ganglia and cerebellum and may reach the internal capsule and the thalamus, regardless the etiology[1,3]. The reason for this tropism is unknown, but recent findings suggest that cellular and histochemical specificities, such as vascular permeability and the presence of other electrolytes (iron, zinc and magnesium), may contribute to the process[3-5]. CC development is slow and may remain asymptomatic for long periods of time[3,4].

The principal causes of CC are shown in table 1. Pathologies most statistically associated to CC are calcium and phosphorus metabolic disturbances (endocrinopathies and genetic syndromes)[3,4]. Even though uncommon, hypoparathyroidism is a possible cause of severe psychiatric disturbances, whether these be related or not to CC[5]. Parathormone (PTH) deficiency results in a reduction in serum calcium levels and an increase in serum phosphate levels, thus producing mineral deposits in the skin, retina and cerebrum[1]. Clinical symptoms of calcium imbalance previously demonstrated include: tetany, Chvostek sing (facial muscle cramps), laryngeal stridor, muscle stiffness, movement disturbances (freezing), and seizures[1-5]. The last of which may be the only manifestation of this condition[1].

Table 1. Causes associated to cerebral calcification

Parathormone metabolism, calcium and phosphorus		Without sistemic involvement
Injured	**Preserved**	
Hypoparathireoidism	Down syndrome	Idiopathic
Primary	Neuromyophaties mitochondrial	Fahr's disease
Post-surgical	Systemic lupus erythematosus	Diffuse neurofibrillary Tangles with calcification
External radiation	Acute lymphocytics leukemia	Aging/physiological
Hypomagnesemia	Revesz syndrome	
Pseudohypoparathyroidism	Infections: CMV, HIV, neurotoxoplasmosis, EBV	
Hyperparathyroidism	Toxicosis: Lead e CO	

EBV: Epstein-Barr vírus; CO: carbon monoxid; CMV: citomegalovirus; HIV: human immunodeficiency virus.

Neuropsychiatric syndromes are commonly seen when CC are secondary to hypoparathyroidism and tend to be serious problems[1-4]. Acute conditions, such as *delirium*, may derive from electrolytic disturbances, especially in post surgical and toxic forms[1]. Cognitive deterioration is the most common psychiatric symptom resulting from hypoparathyroidism[1]. Mood disorders (anxiety, panic attacks, depression and *neurasthenia*) are frequent and may be the first clinical manifestations of this condition. Symptoms are intermittent, with periods of spontaneous remission[1,3]. The onset of psychotic symptoms tends to occur later and seem to be associated with the calcification of the basal ganglia[3]. Hypothyroidism is commonly part of greater global cognitive impairment, in post surgical hypoparathyroidism.

The objective of this case report is to present some neuropsychiatric aspects related to CC in patients with calcium and phosphorus disturbances. In this case report, the patient was admitted to a psychiatric hospital, with a prior diagnosis of schizophrenia. After clinical investigation, the case revealed to be post surgical hypoparathyroidism with extensive CC. The psychiatric Institution authorized the publication of data gathered for this study.

CASE REPORT

A few weeks after his divorce in 2005, a 52-year-old man began to show signs of behavioral disorder, specifically social withdrawal, functional impairment and aggressiveness, associated to psychotic symptoms (persecutory delusions and hallucinations involving imperative voices). He was diagnosed as schizophrenic (paranoid subtype) and achieved satisfactory symptomatic control during outpatient psychiatric treatment, at that time. However, from 2006 onwards, he developed cognitive impairment and movement disorders. These symptoms weakened his adherence to treatment and resulted in several psychiatric hospitalizations, always triggered by psychotic relapse symptoms (delusions, hallucinations and psychomotor agitation). Yet his response conventional antipsychotic therapy was positive.

In June 2009, the patient was admitted to a psychiatric hospital to better evaluate the general deterioration of his condition. He was dehydrated, malnourished, showed psychomotor retardation, choreoathetotic appendicular and orolingual movements, myoclonias, pancerebellar ataxia, pyramidal signs, paratonia and Chvostek sing. A clinical exam of other organic systems came up normal, except for hypotension (100/70 mmHg). The laboratory investigation came up normal, except for: PTH < 3 pg/ml; TSH = 64,5 µUI/ml; T4-L = 0,15 ng/dl; Ca^{++} = 0,65 mmol/L and phosphorus = 47 mg/dl. The cranial CT scan revealed extensive CC (Figure 1).

While taking the psychiatric examination, the patient remained awake, with hypoprosexia, temporal and spatial disorientation, hypokinesia and upper stereotyped movements. He showed no response to external stimulation nor to simple verbal commands and sometimes became restless when hearing his name. He was unable to speak complete words, babbled unspecific sounds and did not seem to understand the examiner's questions. A decrease in displays of affectivity and inaccessible memory were also verified. No hallucinato-

ry attitude was observed. The application of neurocognitive tests such as MMSE (Mini Mental State Exam), were unsuccessful because of his global cognitive deterioration.

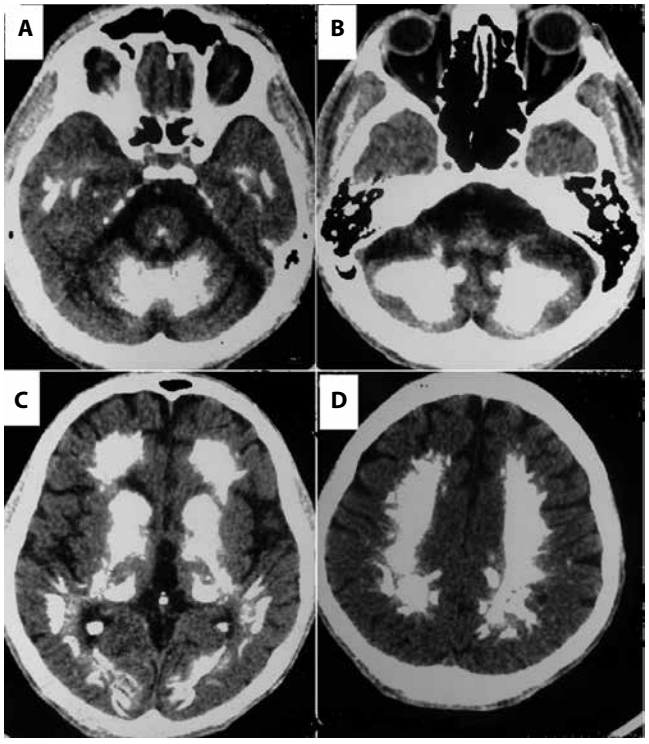

Figure 1. Brain CT revealing extensive calcification of: A) Cerebellar anterior lobe; midbrain; temporal periventricular white matter. B) Cerebellar white matter, including inferior cerebellar peduncles; cerebellar amygdale. C) White matter of frontal, parietal and occipital gyri, including U-fibers; internal capsule; caudate, lentiform and thalamus nuclei; choroid plexus and pineal. D) centrum *semiovale*.

An investigation of his prior medical history revealed a Papilliferous Carcinoma of the Thyroid, treated with total resection in 1986. His post-surgical control and treatment in an outpatient endocrinological clinic was irregular and the patient abandoned the treatment altogether, at the onset of psychiatric symptoms. It has been verified family history of schizophrenia on his maternal grandparents.

During his psychiatric admission (17 days), the patient received adequate nutritional support, the correction of electrolytic disturbances and calcium and phosphorus reposition (1 g/day and 10 µg/day, respectively). He also started T4-L reposition (12,5-25 mg/day) and his insomnia was successfully treated with clonazepam. Despite the treatment adopted, cognitive deficits reminded, such as severe dementia syndrome (aphasia, alogia, temporal and spatial disorientation and movement disorders). In light of the complexity of the case, he was transferred to a general hospital. His final diagnosis, after clinical investigation, was Dementia in hypercalcemia (Dementia in other specified diseases classified elsewhere, F – 02.8, by ICD-10).

DISCUSSION

Our case report seeks to highlight the importance of excluding general medical and/or substance related conditions whenever a psychiatric condition appears. We also look into an extreme case of extensive CC, derived from iatrogenic hypoparathyroidism. The "*exclusion of substance/general medical condition*", proposed by DSM-IV and ICD-10, is mandatory for all psychiatric diagnoses, even though clinical components and family history are standard of primary mental disorders.

The patient's initial clinical manifestations consisted in a delusional-hallucinatory syndrome, with characteristics of paranoid schizophrenia, and he also had a positive family history of mental disorder. The atypical characteristics of his syndrome were the absence of a premorbid personality and the late onset, in his fifties. The post surgical hypoparathyroidism and the period of time that elapsed until the onset of psychiatric symptoms are compatible with the patient's clinical condition, as well as the laboratory and imaging findings[1,3-5]. However, it's likely that hypothyroidism contributed to the patient's cognitive-motor neurological condition. Seizures and signs of tetany could be seen in most of the cases described[3,4,6,7], yet our patient only manifested the latter.

Despite the protective effect of the blood-brain barrier, the sub cortical nuclei are vulnerable to impregnation by minerals such as copper (Wilson's disease), iron (neurodegeneration associated with pantothenate kinase) and calcium[3,4,8]. CC occurs in several clinical conditions (Table 1) and may commonly be classified as part of three main groups: Idiopathic, Familial and especially calcium and phosphorus metabolic disorders[1]. Among the latter, the more prominent metabolic disorder are the results of endocrine etiologies, such as hypoparathyroidism, including the most regularly occurring post-surgical/iatrogenic type[3,5]. Calcifications are usually located at the basal ganglia, dentate, thalamus and semioval center[1]. Extensive CC and/or CC located in other cerebral locations are rare, such as in the case report presented here[3,6,7,9,10]. In cases of primary hypoparathyroidism, calcifications tend to be diffuse, while in secondary hypoparathyroidism they tend to be more localized[3].

Recent histochemical studies have revealed the presence of other chemical elements in these lesions such as copper, zinc, magnesium, aluminum, potassium, iron and calcium. These elements surround the organic matrix and lead to mineralization[3]. Special attention should be given to iron, which is found in higher concentrations in these CC regions and apparently increases local dopaminergic neurotransmission[3].

Clinical manifestation seems to vary according to the patient's age at the onset of the calcification process: from 20 and 40 years of age symptoms are predominantly manifested as schizophreniform psychosis, with no neurologi-

cal signs[3]. When the onset occurs after 49 years of age, the psychosis is often accompanied by disorders of movement and dementia[3]. Psychotic symptoms characterized by paranoid delusions, auditory hallucinations (sometimes musical), complex visual hallucinations, hiker behavior and catatonic states, were reported within this age range[3,5]. The extension of the calcification and the severity of the neuropsychiatric symptoms are directly correlated, even though they bear no relationship to any specific kind of symptomatology[3]. Our patient developed belated psychiatric symptoms and had already been diagnosed with dementia, close to the kind of outcomes found in literature on the subject[6,11]. In most patients the prognosis is negative, with permanent cognitive and behavioral damage[6,7,11,12]. Similar case reports have been found for patients with Fahr's disease[6].

Treatment of the underlying cause, when possible, can improve neuropsychiatric symptoms, yet rarely stops the progression of CC[3-5]. Clinical intervention in electrolytic disturbances and intoxications is mandatory. The theoretical benefit of using chelating agents (deferoxamine, penicillamine) has not been proven by clinical studies up to this date[2,4]. In cases of hypoparathyroidism, calcium reposition (1-2 g/day), together with vitamin D (calcitriol, cholecalciferol) is recommended, in order to maintain serum calcium levels at 8-8.5 mg/day and urinary calcium under 200 mg/day[2,4]. The psychotic symptoms may not respond to antipsychotic medication. Lithium carbonate is recommended for refractory patients[1].

CONCLUSION

Mental disorders derived from organic causes are generally reversible, if the appropriate treatment is started early on in the process. Metabolic disturbances linked to calcium and phosphorus are potential causes of severe neuropsychiatric syndromes and permanent cognitive damage. Excluding organicity is mandatory in any psychiatric diagnosis investigation.

INDIVIDUAL CONTRIBUTIONS

Leonardo Fernandez Meyer – Responsible for the data collection, analysis, revision, bibliography and copy-editing the article.
The other authors helped with the bibliography, discussions on the theme and final copy-editing.

REFERENCES

1. David AS, Fleminger S, Kopelman M, Lovestone S, Mellers J. Lishman's Organic Psychiatry. 4th ed. Oxford, UK: Wiley-Blackwell; 2009.
2. Aminoff MJ. Neurology and clinical medicine. 4th ed. New York: Churchill Livingstone, 2004.
3. Casanova MF, Araque JM. Mineralization of basal ganglia: implications for neuropsychiatry and neuroimaging. Psychiatry Res. 2003;121:59-87.
4. Manyam V. B. What is and what is not Fahr's disease. Parkisonism Relat Disord. 2005;11:73-80.
5. Cardeal JO, Cardeal DD. Calcificação simétrica dos gânglios da base (CSGB), "Doença de Fahr". Rev Neurociências. 1999;7(1):28-31.
6. Chabot B, Roulland C, Dollfus S. Schizophrenia and familial idiopathic basal ganglia calcification: a case report. Psychol Med. 2001;31(04):741-7.
7. Shirahama M, Akiyoshi J, Ishitobi Y, Tanaka Y, Tsuru J, Matsushita H, et al. Case report: a young woman with visual hallucinations delusions of persecution and a history of performing arson with possible three generation Fahr disease. Acta Psychiatr Scand. 2010;121:75-7.
8. Blanco P, Viallard J, Ellie E, Faure I, Mercie P, Pellegrin J, et al. Extensive brain calcifications in systemic sclerosis. J Neurol Neurosurg Psychiatry. 1999;67:697a-8a.
9. Castro ML, Borba VZC. Síndrome de Fahr e distúrbios do metabolismo do cálcio. Rev Neurociências. 1999;7(01):22-7.
10. Lauterbach EC, Cummings JL, Duffy J, Coffey CE, Kaufer D, Lovell M, et al. Neuropsychiatry correlates and treatment of lenticulostrial diseases: a review of the literature and overview of research opportunities in Huntington's, Wilson's, and Fahr's diseases. J Neuropsychiatry Clin Neurosci. 1998;10(03).
11. Levy G. Basal ganglia calcification (striopallidodentate calcification) and cognitive impairment. Arqu Neuropsiquiatria. 1999;57(1):148.
12. Montenegro AC, Gelenske T, Carvalho EH, Bandeira F, Sougey E. First description of pseudohypoparathyroidism with frontal lobe calcification and normal serum calcium at the initial manifestation in an otherwise healthy seven-year-old girl. Arq Bras Endocrinol Metabol. 2011;55(05).