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THE SPECTRUM OF COMPUTERIZED TOMOGRAPHY (CT) FINDINGS IN CENTRAL NERVOUS SYSTEM (CNS) INFECTION DUE TO *Cryptococcus neoformans* VAR. *gattii* IN IMMUNOCOMPETENT CHILDREN

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SUMMARY

Cranial CT scans of eleven immunocompetent children with central nervous system (CNS) infection due to *Cryptococcus neoformans* var. *gattii* were retrospectively reviewed. These children had an average age of 8.8 years and positive culture for *C. n.* var. *gattii* in cerebrospinal fluid. The most common signs and symptoms were headache, fever, nuchal rigidity, nausea and vomiting. No normal cranial CT was detected in any patient. Hypodense nodules were observed in all patients . The remaining scan abnormalities were as follows: nine had diffuse atrophy, six had hydrocephalus, and five had hydrocephalus coexistent with diffuse atrophy.

KEYWORDS: Cryptococcosis; *Cryptococcus neoformans*; *Cryptococcus neoformans* var. *gattii*; Childhood; Meningitis.

INTRODUCTION

On the basis of biochemical studies, the asexual anamorph state of *Cryptococcus neoformans* can be divided into two varieties: *C. neoformans* var. *neoformans* (serotypes A and D) worldwide distributed is isolated from soil contaminated with avian feces, in urban areas; occurs in immunosuppressed patients (opportunistic pathogen). *C. neoformans* var. *gattii* (serotypes B and C) occurs mainly in tropical and temperate climates, in soil with eucalyptus trees; has a propensity for causing disease in immunocompetent hosts (primary pathogen)[4,10,15].

Cryptococcosis is an infrequent opportunistic pediatric infection[2,12-14]. A 10-year point prevalence of cryptococcosis among HIV-infected children was of 1.4%[1]. However, the Northeastern Brazilian region is a highly endemic area of cryptococcosis in children due to var. *gattii* [5].

The lesions revealed by cranial CT scans of 11 children under 13 years of age, living in the State of Pará and affected by cryptococcosis of the CNS will be herein presented. Some comments on epidemiology of the disease will also be made.

PATIENTS AND METHODS

The cranial CT scans of eleven children under 13 years of age were retrospectively reviewed. All children had proven CNS infection caused by *C. neoformans* var. *gattii*. CT scan was obtained at least at the time of the diagnosis. They had been brought to hospital between January 1992 and December 2000.

The exams were performed by two different equipments, Toshiba TCT500S and Siemens Somatom AR. A protocol routine to infant was used, with 5 mm collimation in posterior fossae and 10 mm in the upper parts. Intravenous contrast agent was used routinely. All exams were reviewed by one radiologist (KI) that considered any the abnormalities found, with special attention to the presence of abnormalities in densities, mass effect, atrophy, and ventricle sizes.

CNS cryptococcosis infection was recognized by the detection of encapsulated yeasts at the microscopic examination and by the isolation in culture from the cerebrospinal fluid. The variety of the agent was identified by the characteristic color reaction produced by the fungus in the canavanine-glycine-bromothymol blue agar medium[7].

RESULTS

Eight patients were boys and three were girls aged 6 to 12 years old (average 8.8). The most common present signs and symptoms (Table 1) were headache, fever and nuchal rigidity (n = 11); nausea and vomiting (n = 10). The average time from the onset of the symptoms to the diagnosis was 5.2 weeks (ranging two weeks to three months). All the eleven patients presented abnormalities in their cranial CT (Table 2). Hypodense nodules were observed in all of them. The remaining scan abnormalities were as follows: nine had diffuse atrophy, six had hydrocephalus, and five had hydrocephalus coexistent with diffuse atrophy (Figs. 1-3).

There was no correlation between CT findings and the severity of the disease or outcome.

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Table 1
Cerebral nervous system presenting symptoms and cerebrospinal fluid findings

No.	Age, gender	Signs or symptoms; course prior to diagnose	Cerebrospinal fluid		
			White cell count (µl)	Protein (mg/dl)	Glucose (mg/dl)
1	6, F	H, F, NV, NR, S; 5 weeks	15	40	15
2	8, F	H, F, NR, S; 2 months	54	74	10
3	11, M	H, F, NV, NR, VD; 2 weeks	13	35	42
4	12, F	H, F, NV, NR, AMS; 2 weeks	19	37	30
5	9, F	H, F, NV, NR, S, AMS; 3 weeks	10	35	40
6	8, F	H, F, NV, NR, S, AMS; 2 months	46	301	35
7	10, F	H, F, NV, NR; 1 month	930	70	56
8	8, M	H, F, NV, NR; 5 weeks	85	51	68
9	8, M	H, F, NV, NR, VD, S; 2 weeks	299	65	38
10	6, M	H, F, NV, NR; 5 weeks	355	43	51
11	11, M	H, F, NV, NR, S, AMS; 3 weeks	32	141	5

H, headache; F, fever; AMS, altered mental status; VD, visual disturbace; S, seizures; NV, nausea and vomiting; NR, nuchal rigidity;

Table 2
Clinical characteristics and cranial CT scan of children with CNS infection due to *C. neoformans* var. *gattii*

No.	Additional sites of cryptococcal infection	Associated disease	Cranial CT findings	Treatment (*); maintenance	Outcome; complication
1	None	Sepsis	Hypodense nodules, hydrocephalus, and diffuse atrophy	AmB (2 m)	Died
2	Lung pneumonia	None	Hypodense nodules and hydrocephalus	AmB, V-P shunt (7m); Flu	Cured; blindness
3	Bilateral lung masses	Sepsis	Hypodense nodules, hydrocephalus, and diffuse atrophy	AmB, 5-FC, (7m); Flu	Cured
4	None	None	Hypodense nodules and diffuse atrophy	AmB, 5-FC, (3m); Flu	Cured; blindness
5	None	Bacterial pneumonia	Hypodense nodules and diffuse atrophy	AmB, 5-FC (1m)	Died
6	None	None	Hypodense nodules and diffuse atrophy	AmB, 5-FC, V-P shunt (4m); Flu	Cured
7	None	None	Hypodense nodules and diffuse atrophy	AmB (3m); Flu	Cured
8	None	Pulmonary tuberculosis	Hypodense nodules, hydrocephalus, and diffuse atrophy	AmB, V-P shunt (2m); Flu	Cured; blindness
9	None	None	Hypodense nodules	AmB, V-P shunt (3 m); Flu	Cured; blindness
10	None	None	Hypodense nodules, hydrocephalus, and diffuse atrophy	AmB (3m); Flu	Cured
11	None	None	Hypodense nodules, hydrocephalus, and diffuse atrophy	AmB, V-P shunt (3m); Flu	Cured; blindness

AmB, amphotericin B; Flu, fluconazole; 5-FC, flucytosine; V-P, ventriculoperitoneal
(*) Time in months of hospitalization using AmB with or without 5-FC; survivors received maintenance therapy with Flu, as outpatient.

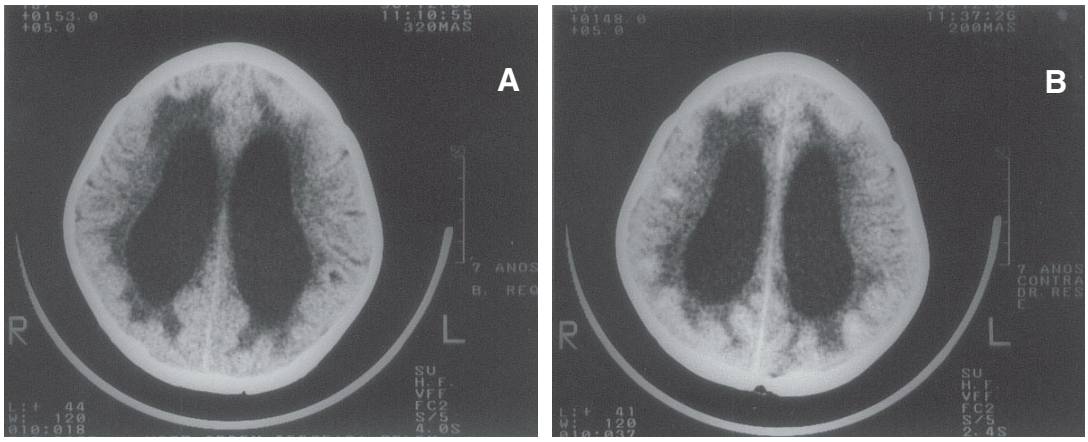

Fig. 1 - Axial CT scan from case 2. (A) Unenhanced CT scan showing hydrocephalus and hypodensity of the cerebral white matter. (B) Contrasted-enhancing CT scan shows that multiple nodules became hyperdense following contrast administration.

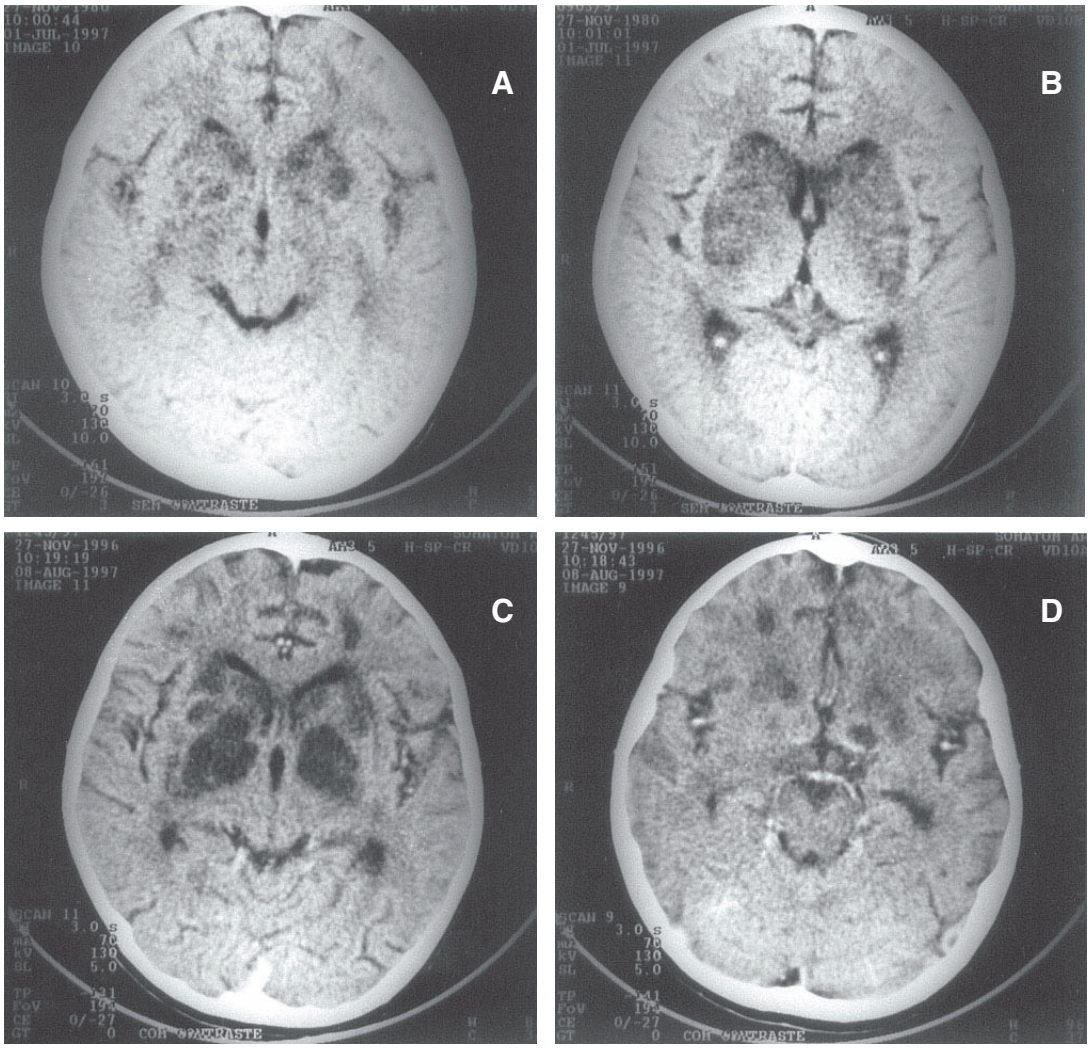

Fig. 2 - Serial axial CT scan from case 3. (A, B) At the diagnosis (01.07.97) CT shows hypodense nodules and mass effect with deformation of the lateral ventricles. (C, D) One month later (08.08.97), following treatment, CT showing hypodensity and mass effect involving the caudate nucleous, globus pallidus, putamen, and internal capsula.

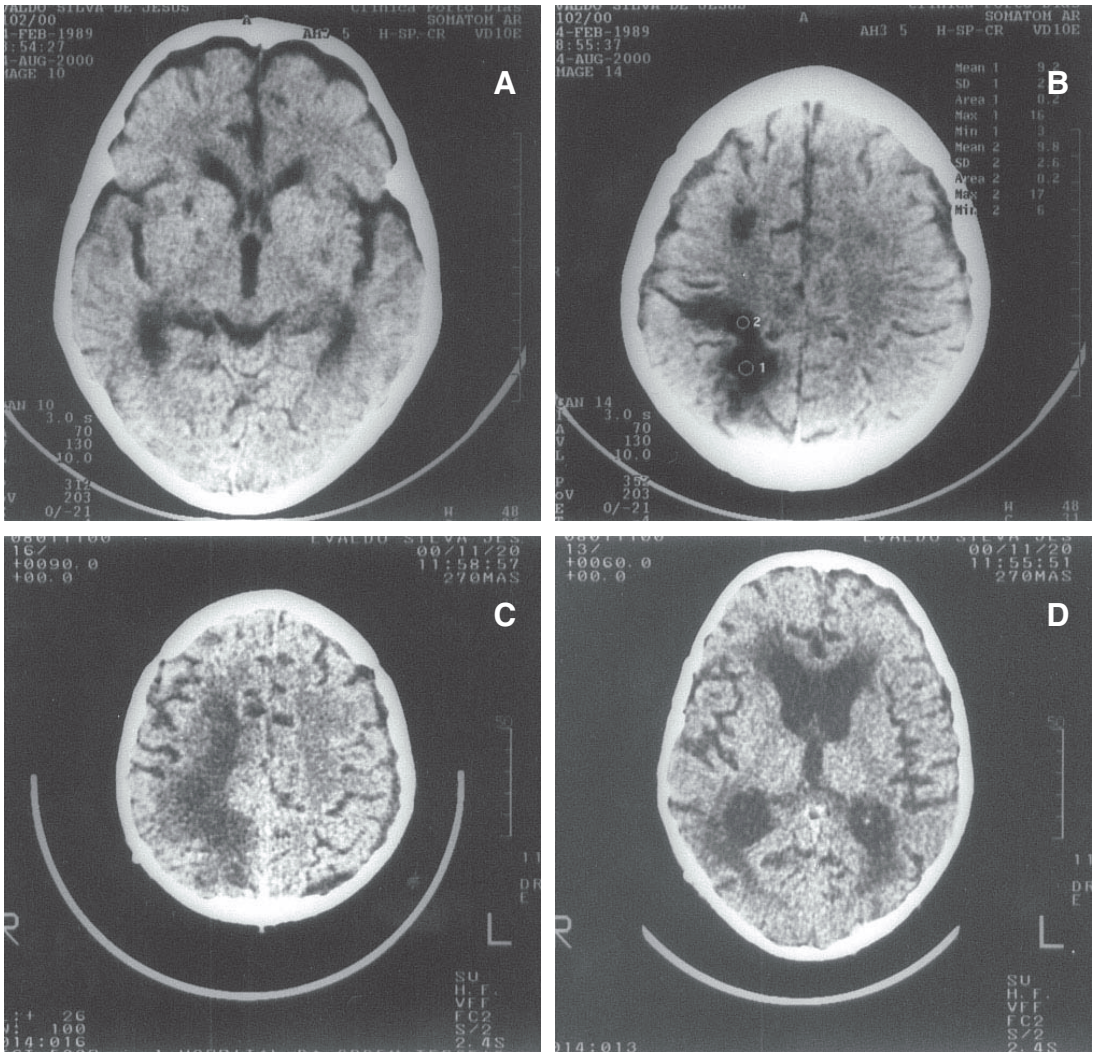

Fig. 3 - Serial axial CT scan from case 11. At the diagnosis (24.08.00) (A) hypodenses nodules in the basal ganglia with mild hydrocephalus and (B) focal area of hypodensity with larger attack of the cerebral white matter. Three months later (20.11.00), following treatment, CT shows (C,D) progression of the attack to the white matter and cerebral diffuse atrophy.

TREATMENT AND OUTCOME

Nine patients were cured after an induction course of amphotericin B (1 mg/Kg/day) with or without 5-fluocytosine (100 mg/Kg/day given as four divided doses at 6-hr intervals) for 2 to 7 months; then, therapy with fluconazole (200 mg/day) was given for maintainance. The remaining two patients died within two months of antifungal therapy. The average cumulated dose of amphotericin B was 1 g. To control increased intracanial pressure, a short course (one week) of dexamethasone therapy (a daily dose of 0.6 mg/Kg in four divided doses) was used in combination with mannitol (1 g/Kg) infused over 30 min, and repeated when necessary at 6- to 8-hr intervals; ventriculoperitoneal shunt was performed in five patients. In five cured patients (56%), blindness was the major complication.

DISCUSSION

The Northeastern and the Northern Brazilian regions are endemic areas of infections caused by *Cryptococcus neoformans* var. *gattii*. CAVALCANTI[3] collected 124 cases of neural cryptococcosis in a nine year period (1986-1995) in the Northeastern region. Seventeen of these patients (13.7%) were children under 10 years of age. Only 45 isolates of the 124 patients were typed, 32 of them were var. *gattii*. In the State of Pará CORREA *et al.*[5] reported 19 cases of cryptococcosis of the CNS in children under 13 years of age, diagnosed in a six year period (1992-1998). The isolates of the last nine patients were typed, all of them, were var. *gattii*. With one exception, these nine patients lived in rural areas resultant of deforestation of the Amazon forest. Epidemiological, clinical, predisposing conditions, therapeutic measures and outcomes were tabulated.

To our knowledge we report the first series of cases of CNS infection due to *C. neoformans* var. *gattii* in immunocompetent children documented by cranial CT scan. This study shows that the most common evident lesion is multiple hypodense nodules, mainly located in the basal gangliar region and in the cerebral white matter. Apparently

these lesions can progress to atrophy of the cerebral white matter, associated with ventricular dilatation and prominence of cerebral sulci, with compensatory hydrocephalus or due to hypertension. Mild changes in the cerebral cortex were observed. Neurological sequelae were frequent in the survival patients.

In this series, the lesions diminished in size or disappeared with medical therapy. These findings are an indicative of the reversibility of the lesions in some cases. Neurological permanent defects were observed in the majority of the survivors. This is a characteristic of var. *gattii* in healthy hosts, including adults[15] .

CNS is the most common involved site in cryptococcosis[2,4,10,15]. *C. neoformans* has affinities for it; this special tropism is due to the nutritional requirements of the fungus, since the exact and optimal nutritional needs can be supplied by the cerebrospinal fluid[8] and tissue of the region of basal ganglia[4]. But the two varieties of the fungus (var. *gattii* and var. *neoformans*) presented some differences in the nature of CNS involvement. These differences were pointed out in studies of series of patients living in Australia and New Zealand[4,10,15]. However, in these countries where cryptococcosis due to var. *gattii* is endemic, the disease rarely occurs in children[16]. Nevertheless, in the Brazilian Northeastern and Northern regions, specially in the State of Pará, where cryptococcosis by var. *gattii* is also endemic, the disease in children is relatively frequent. The need to understand this frequence and also the nature of CNS involvement deserves more studies in these regions.

Regarding the frequency of abnormalities in the CNS detected by CT, it must be considered as an important tool to analyse the distribution and intensity of lesions as well as treatment response.

Finally, the correlation of cryptococcal intracerebral lesion and outcome requires further study. In this way we suggest a low dose contrast-enhanced CT scan[6,11] or, whenever possible, magnetic resonance images (they give contrast resolution that far exceeds that of CT)[9].

RESUMO

O espectro de achados tomográficos na infecção do SNC por *Cryptococcus neoformans* var. *gattii* em crianças imunocompetentes

Os achados tomográficos de 11 crianças imunocompetentes com infecção do sistema nervoso central por *Cryptococcus neoformans* var. *gattii* foram revisados. Estas crianças tinham uma média de idade de 8,8 anos e cultivo positivo do líquor para *C. neoformans* var. *gattii*. Os sinais e sintomas mais comuns foram cefaléia, febre, rigidez de nuca, náusea e vômitos. Todas as tomografias de crânio foram anormais. Em todos os pacientes foram observados nódulos hipodensos. As demais anormalidades tomográficas foram: 9 pacientes com atrofia cerebral difusa, 6 pacientes com hidrocefalia e 5 com associação de hidrocefalia e atrofia cerebral difusa.

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