Arq Neuropsiquiatr 1997;55(1):122-125

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IN A CHILD WITH ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

ALEXANDRA PRUFER DE Q. C. ARAUJO, HELOISA S. PEREIRA**, RICARDO H. OLIVEIRA***, ANA C. FROTA***, JOSÉ C. ESPERANÇA*, FRANCISCO DUARTE*****

ABSTRACT - Progressive multifocal leukoencephalopathy is a rare viral-induced demyelinating disease associated to immunodeficiency. A 10-year-old boy with AIDS is reported, who developed subacute cerebellar signs and symptoms with multiple cranial nerve involvement and dementia. A computed tomography scan revealed a focal nonenhancing area of low attenuation in the cerebellum. On magnetic resonance imaging high signal lesions in T2 weighted sequences were shown. The biopsy of one of those lesions showed the typical histological findings of progressive multifocal leukoencephalopathy. It seems important to consider this diagnosis in children with AIDS who present with progressive neurological features.

KEY WORDS: progressive multifocal leukoencephalopathy, acquired immunodeficiency syndrome, children, diagnosis.

Leucoencefalopatia multifocal progressiva em uma criança com síndrome da imunodeficiência adquirida

RESUMO - A leucoencefalopatia multifocal progressiva é uma doença desmielinizante rara, induzida por vírus em indivíduos imunodeficientes. Relata-se o caso de um menino de 10 anos de idade com síndrome da imunodeficiência adquirida (SIDA), que desenvolveu quadro subagudo de sinais e sintomas cerebelares com acometimento de nervos cranianos e demência. A tomografia computadorizada de crânio mostrou uma área de hipodensidade não captante no cerebelo. A ressonância magnética evidenciou áreas de hipersinal na sequência em T2. A biópsia de uma destas lesões revelou os achados histológicos típicos da leucoencefalopatia multifocal progressiva. Esta hipótese, portanto, deve ser considerada em crianças com SIDA que apresentem deterioração neurológica progressiva.

PALAVRAS-CHAVE: leucoencefalopatia multifocal progressiva, síndrome da imunodeficiência adquirida, criança, diagnóstico.

Opportunistic infections gained remarkability after the beginning of AIDS epidemics in the early eighties. Progressive multifocal leukoencephalopathy (PML) is a demyelinating condition, related to papova JC virus infection in immunosuppressed patients, which carries a very poor prognosis. It has rarely been seen in children, either with severe inherited immunodeficiencies[15,26], or with AIDS[7,17,24]. Nowadays the main cause of immunodeficiency associated with PML is AIDS[7]. Although human immunodeficiency virus (HIV) infection is increasing in children, only a few cases of PML in this population have been reported, reason for the presentation of this case.

CASE REPORT

A ten year old boy (EMT) was diagnosed as HIV infected in November 1991. Parents were HIV negative and his risk factor was having had a transfusion as a neonate due to pneumonia. He was started on zidovudine

Child Neurology and Infectious Diseases Units of the Department of Pediatrics, and Department of Pathology, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil: * M.D., M.Sc., Assistant Professor; ** M.D., Postgraduate in Neuropediatrics; *** M.D., Pediatrician; **** M.D., Professor. Aceite: 24-outubro-1996.

Dra. Alexandra Prufer Araujo - Rua Gildásio Amado 55/211 - 22631-020 Rio de Janeiro RJ - Brasil.

(AZT) at 180 mg/m2, in November 1991. He had severe leukopenia and anemia which did not disappear in a lower dose scheme. Treatment was discontinued in July 1992. He had no neurological symptom or sign and his computed tomography scan (CT-scan) was normal up to October 1992. At that time he started to have a feeling of unsteadiness, occasional headaches and fatigue. On neurological examination an asymmetric cerebellar syndrome was depicted, more remarkably on his left side; in addition, a diminished vibration sense in the four limbs was detected. He was submitted to nerve conduction studies, which were normal, and a CT-scan which showed a hypodense area on the posterior fossa without edema or contrast enhancement.

One month later he developed nausea, drowsiness and facial paresthesiae on the left side. On that occasion, besides the previous findings, he had also involvement of the facial and trigeminal cranial nerves on the left side. A cerebrospinal fluid (CSF) examination showed no cells, protein content of 43 mg/dl, 80 mg/dl of glucose and no evidence for mycobacteria or fungi. Magnetic resonance image (MRI) showed a focal high T2 signal lesion in the cerebellum and brain-stem.

Two months after the neurological symptoms started he became aphasic, had involvement of the abducent cranial nerve on the left and dysphagia, in addition to his other neurological manifestations. A brain biopsy was then performed which disclosed an astrocytic proliferation with bizarre and atypical forms, besides enlarged oligodendroglia with typical nuclear inclusion bodies (Fig 1).

His condition continued to deteriorate, becoming bedridden, unable to speak, with difficulties swallowing and finally dying 3 weeks after the biopsy.

DISCUSSION

PML is due to the infection of JC virus, a papovavirus (papilloma, polyoma, vacuolating viruses). This is a small, simple, DNA virus that establishes long term persistent infection in humans. Primary infection is probably asymptomatic, with persistence of the viruses in the kidney and in B lymphocytes[9]. Although seroconvertion to this virus takes place early in life[23], the nervous system disease, usually of adult onset, only occurs as a reactivation of the infection in conditions associated with T-cell immunodeficiency[22]. Infected B lymphocytes transport JC virus to the brain where it infects oligodendrocytes and astrocytes[19]. The demyelination associated to the disease is due to lysis of the oligodendrocytes. In astrocytes the JC virus causes morphological cell transformation[12].

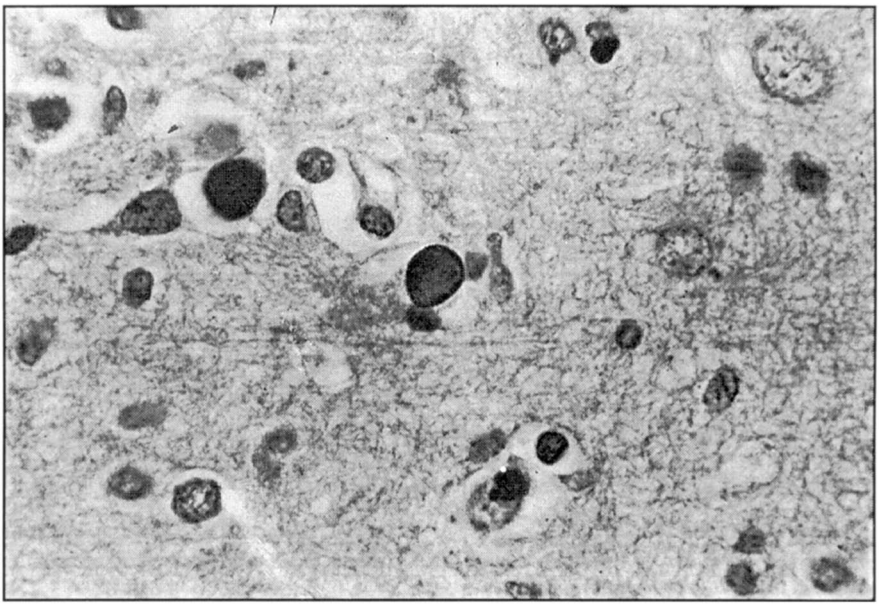

Fig 1. Enlarged oligodendrocyte with typical poliomavirus nuclear inclusion. 400x HE.

In children PML has been described in the setting of inherited immunodeficiency diseases[15,26]. As it is today the most common cause of immunodeficiency, AIDS has been disclosing many conditions once seen very rarely. Between those conditions, PML is starting to be described more often in children due to the increase in the number of HIV infection in this population[7,17,24]. This occurs not only due to the frequency of this severe immunodeficiency, but also to interaction between proteins of both viruses[9,19].

AIDS gives rise to a variety of neurologic findings in children[1], whose pathogenesis is mostly due to the HIV itself[2]. The HIV encephalopathy is frequently observed among infected children and the main findings are those of motor and mental delay or regression, with microcephaly[1,3,11]. Opportunistic infections in this setting are rarer than in the adult population, toxoplasmosis being the most common one in Brazilian children[1].

In adults PML occurs in up to 5% of the patients infected with HIV[4]. In a previous review of 107 cases from 1984, when the AIDS epidemics had just started, only 3% of the PML cases were related to AIDS[8], where as nowadays probably more than 50% are associated with HIV infection[4-6,10]. In adults PML has even been described as the first clinical manifestation of AIDS[6,14].

Signs and symptoms due to the involvement of the cerebral white matter distinguish PML. Visual field defects, focal or generalized limb weakness and ataxia occur frequently at the onset and during the course of the disease. Others, not related to the white matter, include mental deficits and aphasia[4,5,7,14,15,22]. Ataxia was the presenting symptom of our patient, but the extensive brain stem involvement he developed is an unusual finding, although in other two children this has also been described[7,15].

Imaging supports the diagnosis. CT-scan reveals nonenhancing hypodense white matter lesions without mass effect[4,5,7,8,12]. MRI is more sensitive, particularly for small lesions or for those located in the brain stem. It will show patchy or confluent areas of hypointensity on T1 and hyperintensity on T2 weighted images, which can be enhanced with gadolinium[5,6,12,14,15,18]. The lesions tend to occur in the subcortical areas of the parieto-occipital lobes, but may appear elsewhere in the cerebrum, cerebellum, brain stem and spinal cord[5,7,20].

Although some favor the use of serum viral antibodies[16], they are usually not helpful as a diagnostic tool, because such antibodies are common in the general population and, due to the underlying immunosupression, a rise of titers is a rare event[4,8,12].

Lumbar puncture, as was done in our patient, is indicated primarily to exclude other etiologies for the clinical findings. CSF may be completely normal or show a slight increase in protein, rarely lymphocytic pleocytosis or presence of myelin basic protein[5,8,12]. Application of polymerase chain reaction (PCR) to CSF samples is a promising diagnostic tool[4,7,13,19].

Up to now, confirmation of PML requires brain biopsy. Our patient had the characteristic histopathological features: areas of demyelination, enlarged oligodendroglial nuclei with inclusions, bizarre enlarged astrocytes with irregularly multilobulated hypercromatic nuclei. Electronic microscopy, immunostaining, PCR or in situ hybridization on brain specimens may improve diagnostic accuracy[7,8,12,13,15,21].

Although there have been reports of longer survival[6], patients with this condition usually progress to death within a mean of four months[4,5,7,15]. A better prognosis is related to a higher CD4 T lymphocyte count and absence of brain stem involvement[4,6].

Concerning the treatment, many different drugs have been tried: cytosine arabinoside, adenosine arabinoside, camptothencin, acyclovir, prednisone, interferon, and other imunostimulating agents[5,7,8,12,19]. Only the first one is still under study, due to the slight improvement shown in a few patients.

The scarce reports of PML in children with AIDS may be due to the poor survival of HIV infected children or a underdiagnosis of this condition. It should be suspected whenever children with AIDS develop slowly evolving neurological deficits including blindness, weakness, incoordination or language disturbances on top of their basic condition, as this report has illustrated.

REFERENCES

1. Araujo APQC. Neurologic findings in Brazilian children with human immunodeficiency virus infection. Pediatric Aids 1994;5:33-34.
2. Araujo AQC, Araujo APQC, Novis SAP. A neuropatogenia do vírus da imunodeficiência humana. Arq Neuropsiquiatr 1996;54:335-345.
3. Belman AL, Diamond G, Dickson D, Houroupian D, Llena J, Lantos G, Rubinstein A. Pediatric acquired immunodeficiency syndrome: neurologic syndromes. Am J Dis Child 1988;142:29-35.
4. Berger JR, Concha M. Progressive multifocal leukoencephalopathy: the evolution of a disease once considered rare. J Neurovirol 1995;1:5-18.
5. Berger JR, Kaszovitz B, Post MJD, Dickinson G. Progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection: a review of the literature with a report of sixteen cases. Ann Intern Med 1987;107:78-87.
6. Berger JR, Mucke L. Prolonged survival and partial recovery in AIDS-associated progressive multifocal leukoencephalopathy. Neurology 1988;38:1060-1066.
7. Berger JR, Scott G, Albrecht J, Belman AL, Tornetore C, Major EO. Progressive multifocal leukoencephalopathy in HIV-infected children. AIDS 1992;6:837-841.
8. Brooks BR, Walker DL. Progressive multifocal leukoencephalopathy. Neurol Clin 1984;2:299-313.
9. Butel J. Papova viruses. In Kendall RR, Stroop WG. Handbook of neurovirology. New York: Marcel Decker, 1994;339-354.
10. Chimelli L, Rosemberg S, Hahn MD, Lopes MB. Pathology of the central nervous system in patients infected with the human immunodeficiency virus (HIV): a report of 252 autopsy cases from Brazil. Neuropathol Appl Neurobiol 1992;5:478-488.
11. Epstein LG, Sharer LR, Oleske JM, Connor EC, Goudsmit J, Bagdon L, Robert-Guroff M, Koenigsberger R. Neurologic manifestations of human immunodeficiency virus infection in children. Pediatrics1986;78:678-687.
12. Greenle JE. Papovavirus diseases. In Kendall RR, Stroop WG. Handbook of neurovirology. New York: Marcel Decker, 1994:355-367.
13. Henson J, Rosemblum M, Armstrong D, Furneaux H. Amplification of JC virus DNA from brain and cerebrospinal fluid of patients with progressive multifocal leukoencephalopathy. Neurology 1991;41:1967-1971.
14. Jakobsen J, Diemer NH, Gaub J, Brun B, Helweg-Larsen S. Progressive multifocal leukoencephalopathy in a patient without other clinical manifestations of AIDS. Acta Neurol Scand 1987;75:209-213.
15. Katz DA, Berger JR, Hamilton B, Major EO, Post MJD. Progressive multifocal leukoencephalopathy complicating Wiskott-Aldrich syndrome. Arch Neurol 1994;51:422-426.
16. Knight RS, Hyman NM, Gardner SD, Gibson PE, Esiri MM, Warlow CP. Progressive multifocal leukoencephalopathy and viral antibody titres. J Neurol 1988;235:458-461.
17. Krasinski K, Borkowsky W, Holzman RS. Prognosis of human immunodeficiency virus infection in children and adolescents. Pediatr Infect Dis J 1989;8:216-220.
18. Levy JD, Cottingham KL, Campbell RJ, Moore GK, Gyorkey F, Ashizawa T, Goldman AM. Progressive multifocal leukoencephalopathy and magnetic resonance imaging. Ann Neurol 1986;19:399-401.
19. Major EO, Ault GS. Progressive multifocal leukoencephalopathy: clinical and laboratory observations on a viral induced demyelinating disease in the immunodeficient patient. Curr Op Neurol 1995;8:184-190.
20. Mark AS, Atlas SW. Progressive multifocal leukoencephalopathy in patients with AIDS: appearance on MR images. Radiology 1989;173:517-520.
21. Suhrland MJ, Koslow M, Perchick A, Weiner E, Greco MA, Colquhoun F, Muller WD, Burstein DE. Cytologic findings in progressive multifocal leukoencephalopathy: report of two cases. Acta Cytologica 1987;31:505-511.
22. Stoner GL, Walker DL, Webster HF. Age distribution of progressive multifocal leukoencephalopathy. Acta Neurol Scand 1988;78:307-312.
23. Taguchi F, Kajioka J, Miyamura T. Prevelance rate and age of acquisition of antibodies against JC virus and BK virus in human sera. Microbiol Immunol 1982;26:1057-1064.
24. Vandersteenhoven JJ, Ddaibo G, Boyko OB, Hulette CM, Anthony DC, Kenny JF, Wilfert CM. Progressive multifocal leukoencephalopathy in pediatric acquired immunodeficiency syndrome. Pediatr Infect Dis J 1992;11:232-237.
25. Weber T, Turner RW, Frye S, Ruf B, Haas J, Schielke E, Pohle HD, Luke W, Luer W, Felgenhauer K. Specific diagnosis of progressive multifocal leukoencephalopathy by polimerase chain reaction. J Infect Dis 1994;169:1138-1141.
26. Zurhein GM, Padgett BL, Walker DL, Chun RWM, Chorowitz SD, Hong R. Progressive multifocal leukoencephalopathy in a child with severe combined immunodeficiency. N Engl J Med 1978;299:256-257.