Arq Neuropsiquiatr 2001;59(3-B):784-789

REVERSIBLE POSTERIOR LEUCOENCEPHALOPATHY SYNDROME ASSOCIATED WITH BONE MARROW TRANSPLANTATION

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ABSTRACT - Reversible posterior leucoencephalopathy syndrome (RPLS) has previously been described in patients who have renal insufficiency, eclampsia, hypertensive encephalopathy and patients receiving immunosuppressive therapy. The mechanism by which immunosuppressive agents can cause this syndrome is not clear, but it is probably related with cytotoxic effects of these agents on the vascular endothelium. We report eight patients who received cyclosporine A (CSA) after allogeneic bone marrow transplantation or as treatment for severe aplastic anemia (SSA) who developed posterior leucoencephalopathy. The most common signs and symptoms were seizures and headache. Neurological dysfunction occurred preceded by or concomitant with high blood pressure and some degree of acute renal failure in six patients. Computerized tomography studies showed low-density white matter lesions involving the posterior areas of cerebral hemispheres. Symptoms and neuroimaging abnormalities were reversible and improvement occurred in all patients when given lower doses of CSA or when the drug was withdrawn. RPLS may be considered an expression of CSA neurotoxicity.

KEY WORDS: neurological complications, cyclosporine A, bone marrow transplantation.

Leucoencefalopatia posterior reversível associada a transplante de medula óssea

RESUMO - A síndrome de leucoencefalopatia posterior reversível (SLPR) tem sido descrita em pacientes com insuficiência renal, eclâmpsia, encefalopatia hipertensiva e em pacientes que recebem terapia imunossupressora. O mecanismo pelo qual os agentes imunossupressores podem causar a síndrome ainda não são conhecidos, porém estão provavelmente relacionados aos efeitos citotóxicos destes agentes no endotélio vascular. Relatamos oito pacientes que receberam ciclosporina A (CSA) após transplante de medula óssea alogênico ou para tratamento de anemia aplástica severa e que desenvolveram a SLPR. Os sinais e sintomas mais comuns foram convulsões e cefaléia. A disfunção neurológica ocorreu simultaneamente ou precedida por elevação da pressão arterial sistêmica e disfunção renal aguda em seis pacientes. O exame de tomografia computadorizada do crânio demonstrou a presença de áreas de baixos valores de atenuação na distribuição da substância branca, envolvendo áreas posteriores de ambos os hemisférios cerebrais. O quadro clínico e as anormalidades tomográficas foram reversíveis; a melhora ocorreu em todos os pacientes em que as doses de CSA foram reduzidas ou quando a droga foi retirada. A SLPR pode ser considerada uma expressão de neurotoxicidade da CSA.

PALAVRAS-CHAVE: complicações neurológicas, ciclosporina A, transplante de medula óssea.

Allogeneic bone marrow transplantation (AlloBMT) is an important therapeutic option for hematological malignant and non-malignant diseases, some immunodeficiency disorders and certain inborn errors of metabolism. It is associated with several unusual complications[1]. Neurological events are frequent in AlloBMT recipients and they lead to high morbidity and mortality[2], although their frequency and type vary among different series[3]. One of these complications is reversible posterior leucoencephalopathy syndrome (RPLS). The most common symptoms include headache, seizures, visual abnormalities, decreased alertness and altered mental status[4]. Imaging studies demonstrate white matter low density

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Received 21 March 2001, received in final form 25 May 2001. Accepted 31 May 2001.

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areas on computerized tomography (CT) and bright T2-weight signal changes on magnetic resonance imaging (MRI) scan[4,5].

We report eight patients who developed RPLS during the treatment with Cyclosporine A (CSA), utilized for graft versus host disease (GVHD) prophylaxis after AlloBMT.

METHOD

From March 1992 to August 2000, eight patients admitted at our Service presented neurological events and lesions on CT compatible with RPLS after AlloBMT.

The patients received CSA as part of prophylaxes to graft versus host disease (Table 1). They underwent BMT due to severe aplastic anemia (4 patients), chronic myeloid leukemia (2 patients), Fanconi's anemia (1 patient) and myelodysplastic syndrome (1 patient).

CSA levels in plasma were performed routinely on a weekly basis until 8 weeks after the drug starting on all patients, by a fluorescence polarization immunoassay method. In general, CSA levels between 200 – 400 ng/ml were acceptable. CSA levels, when possible, were also measured at the time of suspected drug toxicity. CSA was withdrawn only if neurological toxicity was considered Grade IV (intractable seizures or coma).

RESULTS

The most common present signs and symptoms were seizures and headache (Table 2). Neurological dysfunction occurred preceded by or concomitant with high blood pressure and abnormal renal function in 6 patients undergoing BMT (Tables 2 and 3). One patient also presented hypomagnesemia. CT studies showed low-density white matter lesions involv-

Table 1. Prophylaxis against GVHD.

Disease	Prophylaxis against GVHD
SAA	Intravenous CSA 3 mg/kg twice daily from day -1 until they could be treated with oral medications, at which point oral therapy was started with 12 mg/kg of CSA p.o. This dose was maintained until day +50 and then reduced slowly to 6,25 mg/kg daily on day +180. After that the drug was reduced progressively and discontinued within a year. Intravenous MTX 15 mg/kg once a day on the first day and with 10 mg/kg on days 3, 6 and 11
CML	Intravenous CSA 5mg/kg twice daily from day -1 until +2, 3 mg/kg iv twice daily from day 3 until day 14, 3,75 mg/kg iv from day 15 until day 35, 15 mg/kg per os with progressive reduction from day 36 until day 180. Intravenous MTX 15 mg/kg once a day on the first day and with 10 mg/kg on days 3, 6 and 11. Methylprednisolone 1 mg/kg was administered from day 14 until day 28 and later tapered off.
Fanconi's anemia	Intravenous CSA 3 mg/kg twice daily starting on day -1. Intravenous MTX 15 mg/kg once a day on the first day and with 10 mg/kg on days 3, 6 and 11.
Myelodisplasic syndrome	Intravenous CSA 3 mg/kg twice daily starting on day -1 .

Table 2. Patients characteristics and findings.

# Patient	Age/Sex	Diagnosis / Procedure	Clinical findings
1	27/F	CML / BMT	Hypertension, headache, blurred vision, seizures
2	16/F	SAA / BMT	Hypertension, headache, status epilepticus
3	10/F	FA / BMT	Hypertension, headache, drowsiness, seizures
4	17/M	SAA / BMT	Hypertension, headache, seizures
5	36/F	SAA / BMT	Hypertension, seizures
6	21/F	CML / BMT	Seizures
7	15/F	SAA / BMT	Seizures
8	63/M	MDS / NM-BMT	Hypertension, blindness, seizures

SAA, severe aplastic anemia; CML, chronic myeloid leukemia; FA, Fanconi anemia; MDS, myelodysplastic syndrome; BMT, bone marrow transplantation; IST, immunesuppressive therapy; NM BMT, non-myeloablative bone marrow transplantation.

Table 3. Laboratory features, CT studies and outcome.

Patient	Serum CSA level (ng/ml)	Serum Creatinine level (mg/dl)	Lesions on CT	Improvement on lowering CSA dose	Outcome
1	NR	1.5	Bilateral low density areas involving white matter of temporal-occipital lobes	4 days	Alive, normal neurological status
2	416	2.0	Bilateral low density cortical and subcortical lesions involving parieto-occipital lobes	3 days	Alive, normal neurological status
3	464.47	1.7	Bilateral white matter low density lesions in parieto-occipital lobes	3 days	Died day + 34 , acute GVHD
4	NR	2.4	Low-density lesion in left occipital lobe	3 days	Died day + 66 , acute GVHD
5	NR	1.5	Right low density areas involving white matter on parieto-occipital lobes and left low-density lesion involving frontal lobe	2 days	Alive, normal neurological status
6	540.12	0.8	Bilateral low density lesions on parietal lobes	1 day	Alive, normal neurological status
7	180.83	0.5	Right low density lesion involving occipital lobe	3 days	Alive, normal neurological status
8	350	1.5	Bilateral low density lesions involving occipital lobes	4 days	Alive, normal neurological status

NR, not realized; CT, computerized tomography; CSA, cyclosporine A; GVHD, graft versus host disease.

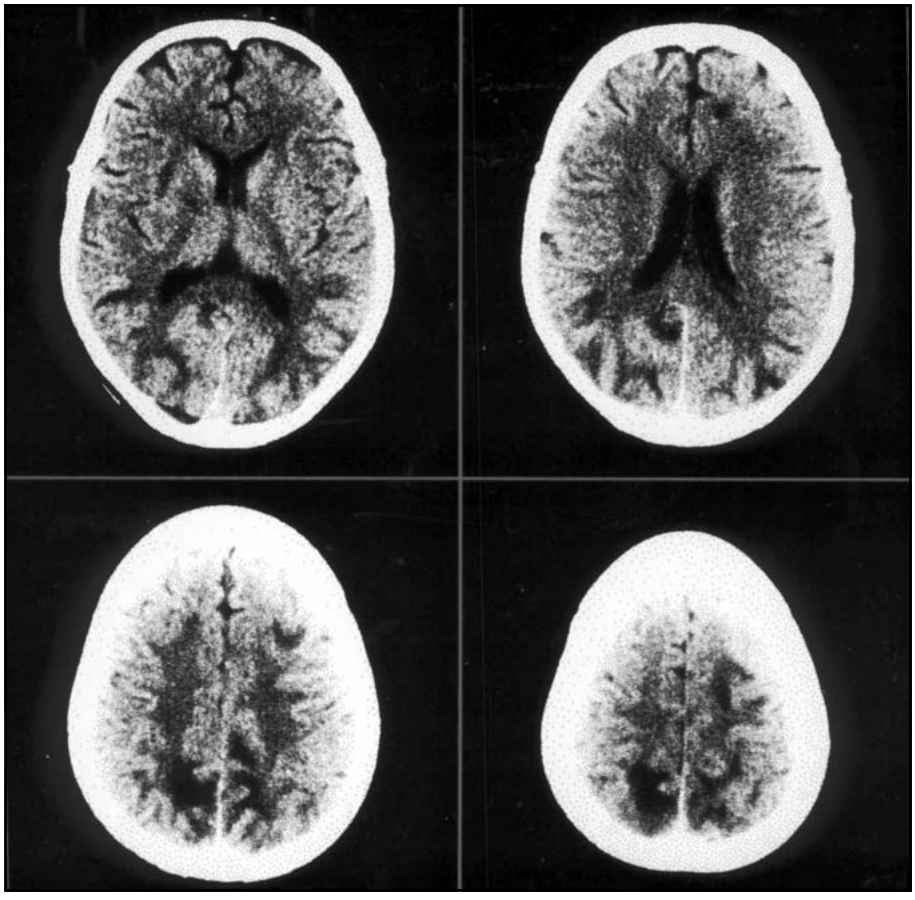

Fig 1. Brain CT of Patient 2 shows low density lesions involving white matter and cortical areas in posterior regions of cerebral hemispheres.

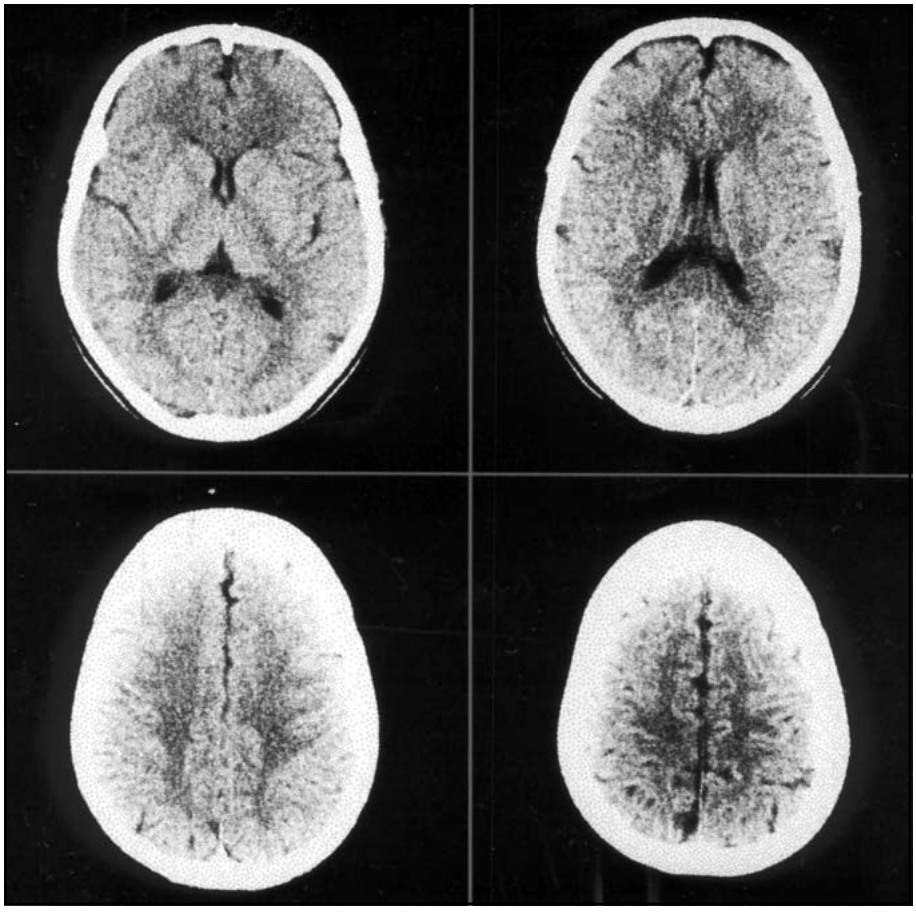

Fig 2. Follow-up brain CT of Patient 2, five months later, shows complete resolution of the previous lesions.

ing the posterior areas of cerebral hemispheres (Table 3). In one patient, follow-up CT scan five months later showed complete resolution of the previous abnormalities (Figs 1 and 2).

Five patients had plasma level of CSA measured at the time of neurological toxicity. It ranged from 180,83 ng/ml to 540,12 ng/ml. Symptoms and neuroimaging abnormalities were reversible. Improvement occurred in all patients, when lowering the dose of CSA (Table 3).

DISCUSSION

BMT is associated with several neurological complications that may be related to underlying diseases, bone marrow transplant procedure and severe immunossupression[6,7]. Allogeneic transplants usually require prolonged immunosuppression and are mostly associated with neurological complications[6]. Cerebrovascular events, central nervous system infections, metabolic encephalopathy and treatment with CSA are the major causes of neurological complications in different series[2-9].

Hinchey et al.[4] reported fifteen patients who developed neurological symptoms and signs associated with reversible white matter lesions in neuroimaging exams characterizing RPLS. This may occur associated with hypertensive encephalopathy, eclampsia, use of recombinant human erythropoietin[10] and use of immunosuppressive agents, mainly CSA. Until the study of Lanzino et al.[5] the morphological substrate of these lesions was hypothesized on the basis of neuroradiological appearance. They reported one patient who underwent stereotaxic biopsy of the lesions. Microscopic examination demonstrated only mildly edematous white matter.

CSA proved to be effective in the prevention and treatment of GVHD[11], the most life-threatening complication after allogeneic BMT[12]. It is also considered part of first line therapy to patients with moderate to severe aplastic anemia[13,14]. CSA is a cyclic undecapeptide of fungal origin, and acts by blocking the release of interleukin-2 and several other cytokines, thereby preventing the second stage of T cells activation[12]. Its use is associated with multiple side ef-

fects and the most common systemic complications are renal and hepatic toxicity and arterial hypertension. Fifteen to 40% of patients receiving CSA also experience neurological side effects[14], like tremor, paresthesia, headache, seizures, confusion, visual hallucinations, cortical blindness, ocular flutter, parkinsonism, cerebellar-like syndromes and leukoencephalopathy[14-17]. Imaging studies demonstrate reversible cortical and white matter low density areas on CT and bright T2-weighted signal changes on MRI[18,19].

The mechanism of these neurological effects is not completely understood. Reports from both in vivo animal models and in vitro endothelial cell cultures suggest that CSA induces endothelial cell injuries[20-22]. Its mediated endothelial cell damage is associated with alteration in the pattern of endothelin, a potent vasoconstrictor, prostacyclin and tromboxane A2 release[22,23]. Elevated plasma levels of endothelin have been found in patients treated with CSA after BMT[24].

Patients with CSA-induced neurotoxicity may also have a disturbance in cerebral blood flow similar to that produced by hypertensive encephalopathy[19]. However, hypertension is not present in all patients with CSA neurotoxicity, such as Patients 6 and 7 of this series. The susceptibility of the posterior regions of the brain to the lesions is not well understood. It is probably related to altered vascular reaction to circulating pressor agents[4], like endothelin, and the relatively poorer sympathetic innervation of posterior circulation[25-26]. Foci of blood brain barrier damage in the occipital and parietal lobes were also demonstrated in patients taking CSA after BMT[27].

The neurological symptoms and signs are reversible when the drug is decreased or withdrawn, but may recur when it is reinstituted. One of our patients (Patient 2) experienced seizure in two different occasions, and in both improvement occurred with decrease of the CSA dose. Resolution of neurological signs and symptoms occurred within four days in all patients of this series.

Associated factors may increase central nervous system toxicity induced by CSA, such as hypomagnesemia, arterial hypertension, acute renal failure, hypocholesterolemia and corticosteroids therapy[4,14,28]. Adverse neurologic events may occur in patients with therapeutic blood levels of the drug and without known risk factors[4,29]. All patients reported in this series were receiving CSA when they developed RPLS; six patients presented arterial hypertension and some degree of renal dysfunction, one also presented hypomagnesemia. The presence of hypomagnesemia also predisposes the patients to neurotoxicity and its prevention seems to reduce the risk of associated neurological dysfunction[29]. One patient had no risk factor other than therapy with corticosteroids. The administration of methylprednisolone associated with CSA increases the risk of generalized seizures, probably secondary to an increase in serum levels of CSA[30-31]. Blood pressure should be closely monitored and elevation treated without delay. Seizures can be treated by magnesium replacement, anticonvulsivants, or preferably, by reduction or withdrawal of CSA. Continuous anticonvulsant therapy is not necessary unless a previous seizure disorder is present.

The reversible posterior leucoencephalopathy presented by these patients may be considered an expression of CSA neurotoxicity. Blood pressure and renal function monitoring and magnesium replacement may help to prevent neurological dysfunction but it is important to be aware that this condition may occur despite therapeutic blood levels of CSA.

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