Short Communication

Posterior leukoencephalopathy syndrome in patients on cyclosporine A treatment following allogeneic hematopoietic stem cell transplantation

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Abstract

Cyclosporine A is widely used as therapeutic agent for immunosuppressive treatment after allogeneic stem cell transplantation. Although several neurotoxic side effects are known the pathogenesis of the involvement of central nervous system remains not fully understood [1-4, 7, 8]. Various clinical manifestations of cyclosporine A toxicity exist with tremor, seizures, neuropathy, visual disturbances or cerebellar ataxia. A reversible posterior leukoencephalopathy syndrome with altered consciousness, seizures, cortical blindness, headache associated with MRI findings of bilateral subcortical and cortical edema with a predominantly posterior distribution is rare but the most serious complication [1, 13].

We report four patients (age 25 – 54 years) who developed a fluctuating psychoorganic syndrome with altered consciousness, disorientation, headache, visual disturbances and seizures under immunosuppressive therapy with cyclosporine A.

Key words: cyclosporine A, immunosuppressive treatment, stem cell transplantation, leukoencephalopathy
two to five months before symptoms occurred (Tab. 1). Neurological examination revealed no focal signs. Hypertension was present in the patients when they were admitted to our intensive care unit. Other laboratory parameters were within normal limits except lymphopenia due to the immnosuppressive therapy. Repeated CSF analysis showed a protein elevation but normal cell count and no signs for infection. EEG only demonstrated general slowing without focal signs nor spikes.

Table.1 Comparison of 4 patients being on cyclosporine A treatment after allogeneic hematopoietic stem cell transplantation in malignant hematological disease.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (sex)</td>
<td>29 (male)</td>
<td>51 (female)</td>
<td>54 (male)</td>
<td>25 (male)</td>
</tr>
<tr>
<td>Underlying hematological disease</td>
<td>CML</td>
<td>CML</td>
<td>CML</td>
<td>Hodgkin’s disease</td>
</tr>
<tr>
<td>Start of symptoms after stem cell transplantation</td>
<td>3 months</td>
<td>4 months</td>
<td>2 months</td>
<td>3 months</td>
</tr>
</tbody>
</table>

Symptoms and findings:

- Altered consciousness and mental functioning: Yes, Yes, Yes, Yes
- Stupor: Yes, Yes, Yes, Yes
- Seizures: Yes, Yes, Yes, Yes
- Headache: Yes, Yes, Yes, Yes
- Visual disturbances: ? , Yes, Yes, ?
- Myoclonus: Yes, No, Yes, No
- Postural tremor: No, Yes, No, No
- Focal neurological signs: No, No, No, No

Clinical Improvement with dose reduction: Yes, Yes, Yes, Yes

(?) Not investigated

Acoustic evoked potentials inconstantly indicated central lesion (prolongation of latency III-V). Somatosensory evoked (medianus nerve) potentials did not show central conduction disturbances. In CT scan there was no focal lesion, only one scan showed cerebral edema in one patient. However, MRI showed in all patients unspecific white matter changes in T2 weighted images predominantly in the posterior region as shown in Fig.1.
Laboratory findings showed no signs for inflammation nor metabolic disturbances. Investigations for bacterial, fungal, viral, cryptococcal and toxoplasmosis infections were negative as well as repeated PCR for JC-virus. The cyclosporine A levels in blood were monitored daily to remain within target range. There was no correlation of serum level to severity of symptoms. Repeated hematological controls of blood did not indicate a relapse of underlying hematological malignancy. Clinical syndrome and neuroradiological findings suggested cyclosporine A neurotoxicity with posterior leukoencephalopathy syndrome. Immunosuppressive treatment was changed according to the hematological findings of underlying disease. With dose reduction or short time withdrawal of the drug in all patients symptoms resolved and did not return. Also MRI changes and disturbances in EEG resolved with clinical improvement. In one patient antiepileptic treatment had to be continued because of reoccurrence of seizures.

Figure 1 MRI of a 51 year old patient suggesting posterior leukoencephalopathy due to cyclosporine A neurotoxicity (T2 weighted images). Symptoms resolved with dose reduction (MRI images by courtesy of Clinic for Radiology, Leipzig University).

One patient died five weeks later because of a nonrelated reason. Here, autopsy revealed unspecific posterior white matter edema, mesial temporal sclerosis on both sides but no vascular changes nor meningeosis lymphomatosa.
In the mentioned cases we considered posterior leukoencephalopathy with typical clinical syndrome and consistent MRI findings in posterior regions only. As in our cases dose reduction or withdrawal usually results in resolution of clinical symptoms and neuroimaging abnormalities (4, 6, 12). However, pathophysiology of posterior leukoencephalopathy remains not fully understood [9, 11]. A reversible vasospasm due to overreaction of brain autoregulation is assumed [1, 12]. An extravasation of fluid and macromolecules into brain tissue caused by an increased blood pressure that overcomes the blood-brain barrier is a favored theory by others [2]. An additional direct neurotoxic effect of cyclosporine A on the blood-brain barrier causing leakage at lower blood pressure is discussed [1, 5, 7, 10]. Also low cholesterol levels might predispose to cyclosporine A neurotoxicity [4]. The posterior pathoclisis of cyclosporine A is still unexplained but typical. Furthermore, clinical manifestation seems to be unrelated to cyclosporine A serum levels [9]. Despite immunosuppression all pathogenetic factors discussed are non infectious. For diagnosis MRI is essential. FLAIR imaging seems to be the most sensitive sequence to detect the characteristic edema of posterior leukoencephalopathy [1]. Since posterior leukoencephalopathy due to cyclosporine A neurotoxicity is a reversible syndrome a dose reduction should be considered in case of characteristic symptoms e.g. coma and seizures [4]. Also low blood levels of cyclosporine A do not exclude a posterior leukencephalopathy. However, our case report also underlies the difficulties in differential diagnosis dealing with immunosuppressed patients. Often the value of laboratory parameters is limited in pancytopenic patients with hematological malignancy. Most of the investigations have to be controlled repeatedly to exclude infectious or metabolic causes for clinical worsening. Possible other neurotoxic effects of antiviral, antimycotic and antibacterial treatment should be taken into account as well. Taken together, our four case histories demonstrate the reversibility of this severe side effect of cyclosporine A.

**REFERENCES**


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