CEREBRAL TOXOPLASMOSIS AFTER RENAL TRANSPLANTATION.

Case Report and Review

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SUMMARY
Infection caused by Toxoplasma gondii is a frequent event in Portugal. When this occurs in immunocompetent individuals, it is rarely a matter of concern; the contrary occurs with immunosuppressed patients or in pregnancy. Transplant patients are treated with immunosuppressive drugs which mainly disturb their mechanisms of cellular immunity, and that opens the way to infections by opportunistic intracellular microorganisms. We recently treated a renal transplant patient who suffered from cerebral toxoplasmosis, and this provided an opportunity for a review of the other 20 patients reported in medical literature to date.

INTRODUCTION

Toxoplasma gondii is a compulsory intracellular protozoan which affects approximately 60% of the Portuguese population above 30 years of age. If the infection is usually contained in the majority of subjects who are immunocompetent without causing great consequences, it can be extremely dangerous in pregnant women and immunodepressed subjects (mainly those with cell mediated immunodeiciencies).

Normally, after initial contact with Toxoplasma gondii, the parasite remains quiescent in cyst form in the different tissues, only to arouse in favourable conditions (in periods of immunodepression), releasing the tachyzoites responsible for the characteristic symptomatology of reactivated toxoplasmosis. One of the organs in which this reactivation has the worst consequences is, without doubt, the central nervous system (CNS). Immuno depressed patients, after the initial infection, disseminated form of the disease may occur immediately.

In HIV infected patients cerebral toxoplasmosis (CT) may occur in approximately 30-50% of those previously infected by the parasite, usually revealing itself when the number of CD4 lymphocytes lowers to values below 100/mm³. In Portugal, a recent study conducted by the Infectious Diseases Department of S. João Hospital, Oporto, indicated its occurrence in 9% of the patients, being the most frequent opportunistic infection of the CNS. The generalised prescription of co-trimoxazole as a primary prophylaxis against Pneumocystis carinii, whenever the number of lymphocytes lowered to values <200/mm³, may currently be responsible for the lower frequency of CT in HIV seropositive patients.

Infection continues to be an important cause of morbidity and mortality in renal transplants and the predominance of intracellular micro-organisms in a certain way reflects the deficient cellular immunity of these subjects. Infections of the CNS may occur in 5 to 10% of patients with renal transplants, revealing itself in the form of acute meningitis (Listeria monocytogenes), sub-acute or chronic meningitis (Cryptococcus neoformans) or focal lesion (Aspergillus spp, Toxoplasma gondii or Nocardia asteroides).

Toxoplasmosis is of particular concern in the case of patients receiving a cardiac transplant, the forms of reactivation being unusual in patients receiving a kidney transplant. One of these patients, whom we had the opportunity of treating very recently, gave the incentive for this paper.

CASE REPORT

Male patient, 42 years of age, with a history of chronic renal insufficiency secondary to angiosclerosis and arterial hypertension. The patient had been on regular haemodialysis since October 1976, receiving a cadaveric kidney on 2nd June 1991. The intervention was successful and the immunosuppression treatment consisted of...
anithymocyte globulin, azathioprine and methylprednisolone. On the second day after the transplant the diagnosis of pneumonia was made, however, it was successfully treated with cefazidime and the patient was discharged on the twentieth day with the instruction to maintain the daily doses of azathioprine (75mg) in association with cyclosporine (120mg) and prednisolone (15mg).

A regular post-transplant follow up was made and no significant complaint was made until 24th April 1992, when a loss of consciousness at work resulted in a fractured clavicle. The patient was taken to the Emergency Department of the Coimbra University Hospitals (CUH), where a neurological examination revealed a slight disartria and labial commissure deviation to the left. A computerised axial tomography (CAT) of the cranium was made (Fig. 1) which showed areas of hypodensity with greater significance in the left temporal-parietal region, which was interpreted as possibly corresponding to a sequela of cerebral ischemia. The patient was referred to the outpatients clinic of the Neurology Department and medicated with glycerol for 5 days. From this date forth the patient began to suffer from progressively worsening headaches until on 17th May 1992, due to intense vomiting, the patient returned to the Emergency Department of the CUH, where he was hospitalised in the renal transplant unit.

Another neurologic observation now revealed central type right facial paresis, disartria and right hemiparesis of brachial predominance; alterations in awareness were not evident, nor were there signs of meningeal irritation. Another CAT of the cranium was made and multiple rounded lesions were visible in both cerebral hemispheres with a distinct enveloping oedema conditioning a mass effect on the adjacent structures, an aspect which was compatible with an opportunist infection.

A specialist in infectious diseases was consulted to give advice about what must be done. It was decided that

![Fig. 1B - CAT of the cranium on 24/4/92 showing hypodensities which are more evident in the left temporal-parietal region.](image)

the patient should be transferred to the Infectious Disease Department in view of the diagnostic possibility of CT. Magnetic resonance (MRI) of the cranium was requested (Figs. 2A and 2B) which confirmed the characteristics of the lesions already shown in the CAT. Treatment was therefore begun with clindamycin (600mg, EV, every 6 hours), pyrimethamine (50mg oral, per day), folic acid (15mg per day) and dexamethasone (5mg, EV, every 6 hours), maintaining immunosuppressive treatment.

Laboratory results showed the patient serologically negative for HIV, hydatidose and cysticercosis. The haemogram was uncharacteristic, E.S.R. 82mm in the 1st hour, creatininemia 1.5mg/dl and the alterations in hepatic function tests were in accordance with the previous diagnosis (August 1990) of chronic hepatitis with cirrhotic evolution attributed to the C virus. The temporal evolution of the serology for Toxoplasma gondii was summarised in Table 1.

![Fig. 2A and 2B - MRI of the cranium performed on 26/5/92 reveals multiple rounded lesions with abundant enveloping oedema.](image)
Table 1 - Temporal evolution of the serology* for Toxoplasma gondii

<table>
<thead>
<tr>
<th></th>
<th>IgG &amp;</th>
<th>IgM</th>
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<tbody>
<tr>
<td>3/6</td>
<td>300</td>
<td>Neg</td>
</tr>
<tr>
<td>20/6</td>
<td>&gt;300</td>
<td>Neg</td>
</tr>
<tr>
<td>20/5</td>
<td>290</td>
<td>Neg</td>
</tr>
<tr>
<td>12/6</td>
<td>200</td>
<td>Neg</td>
</tr>
<tr>
<td>3/7</td>
<td>&gt;300</td>
<td>Neg</td>
</tr>
<tr>
<td>17/8</td>
<td>&gt;300</td>
<td>Neg</td>
</tr>
<tr>
<td>6/11</td>
<td>92</td>
<td>Neg</td>
</tr>
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</table>

* automatic ELISA method; & International units per millilitre (IU/ml)

There was a rapid and clear clinical improvement and a slower improvement in imaging, which led to the decision of maintaining antitoxoplasma treatment for 6 weeks. After this period we decided to begin secondary prophylaxis, with dapsone (100mg, on alternate days) and pyrimethamine (50mg, weekly), which was well tolerated by the patient.

In October 1992, the patient was hospitalised once again due to an episode of focal convulsive fit. MRI of the cranium was repeated (Fig. 3), the lesions were in regression and without signs of activity, only medication with hidantin was advised. Until the first days of January 1993, the evolution has been favourable, good renal function persisting.

REVIEW OF THE LITERATURE

A review of the medical literature available until November 1992 was made with the use of the MEDLINE data base, with the cross reference of the following key words: Cerebral toxoplasmosis and kidney transplantation. The bibliography of the articles found was then exhaustively reviewed and the remaining papers taken from publications which are not indexed.

We made reference of only 20 published cases of CT in subjects with kidney transplants, whose main characteristics are summarised in Table 2. Townsend et al. reported the same case in 1975 (with an error in age) which had already been published by Cohen in 1970.

DISCUSSION

The two most common forms of CT presentation in immunodepressed subjects are (meningo) encephalitis and focal lesion; the latter is frequently found in patients with AIDS, while the former is predominant in patients with transplants. Townsend et al. considered yet a third form, named encephalopathic, with ill defined contours, and which may appropriately be included in diffuse encephalitides. The first case of CT in a patient with a renal transplant was published by Reynolds et al. in 1966, since then another 20 (including the present case) were reported. To date, there has been no reference of any case in Portugal that has been published.

On studying the clinical data of the 21 patients, we observed that the average age was 31.7±12.2 years (interval between 14 and 58) and that males were the most affected, with 13 (68%) of the 19 cases in which these parameters were available.

The average time between transplant and the beginning of symptomatology is closely linked with the immunosuppression protocol and the pathogeny of the infection: longer if it results from a reactivation of the cerebral cystic forms of the parasite and brief if it had been transmitted by the transplanted organ. We are therefore not surprised at the fact that this period has oscillated between 1 day and 7 years, although in 16 (76%) of them the disease occurred in the first 60 days, in accordance with the calendar proposed by Rubin et al.

The transmission of Toxoplasma gondii by the donor’s organ has been proved in renal, hepatic and cardiac transplant, although it is in the latter that it has greater significance. Toxoplasmosis was proved to have been transmitted by the donor in 6 patients and in 4 (including the present case) it most certainly resulted from reactivation; in the remaining 11, due to the omission of decisive data, it is not possible for us to state its pathogeny without doubt. We consider it wise that the procedure which consists of the systematic determination of Toxoplasma immunity in all candidates for cardiac transplant, and the consequent prophylaxis with sulphadiazine and pyrimethamine for 3-6 months in seronegatives who receive an organ from a seropositive donor should, also be implemented in renal transplants.

The alteration of cellular immunity resulting from the immunosuppressive treatment to which transplant patients are subjected, particularly aggressive in the acute phase of the transplant, is responsible for the occurrence of infections by opportunist intracellular microorganisms, among which Toxoplasma gondii. Immunodepression resulting from the use of antithymocyte globulin or CD3 antilymphocytic monoclonal antibodies is particularly severe. The immunosuppressors used on the patients studied were very diversified, although it is agreed that azathioprine and prednisone were the most frequently prescribed.
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<tr>
<td>1966</td>
<td>20/M</td>
<td>1 day</td>
<td>fever, headaches, convulsions, stiff neck</td>
<td>pulmonary oedema</td>
<td>Azathioprine, Prednisone, Cactinomycin</td>
<td>dyes test, Haemaglut.</td>
<td>1/256, 1/64, F. Compl.</td>
<td>1/64</td>
<td></td>
<td></td>
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<td>12</td>
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<td>1967</td>
<td>25/M</td>
<td>56 days</td>
<td>fever, headaches, convulsions, musc. spasms, absences</td>
<td>pneumonia</td>
<td>Azathioprine, Prednisolone, Dactinomycin, Radiation</td>
<td>EEG (slow, temporal &amp; rhythmic)</td>
<td>normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13</td>
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<tr>
<td>1970</td>
<td>35/M</td>
<td>30 days</td>
<td>rejection, transplant, cardiac ins.</td>
<td>pneumonia, abdominal abscesses, cardiac ins.</td>
<td>Azathioprine, Prednisone, Dactinomycin, Radiation</td>
<td>Scintigraphy</td>
<td>(normal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>1970</td>
<td>44/F</td>
<td>28 days</td>
<td>coma, convulsions</td>
<td>pneumonia, anuria</td>
<td>Azathioprine, Prednisone, Methylpred</td>
<td>L-7</td>
<td>N-1</td>
<td>serum</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
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<td>1974</td>
<td>39/M</td>
<td>7 days</td>
<td>alterations in awareness</td>
<td>pneumonia, abdominal abscesses, cardiac ins.</td>
<td>Azathioprine, Prednisone, Methylpred, Cyclophosphamide</td>
<td>EEG (temporal foci)</td>
<td>&gt;P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16</td>
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<tr>
<td>1975</td>
<td>44/M</td>
<td>21 days</td>
<td>hemiparesis, cranial nerve, paresis, fever, alterations in awareness, rash, fever</td>
<td>transplant rejection</td>
<td>Azathioprine, Prednisone, ALG</td>
<td>dyes test, 1/64000, F. Compl.</td>
<td>1/10</td>
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<td>1977</td>
<td>36/M</td>
<td>1 year</td>
<td>transplant rejection, septicemia</td>
<td>pneumonia, retinitis</td>
<td>Azathioprine, Prednisone, Methylpred</td>
<td>L-4</td>
<td>P-142</td>
<td>1/2048 Pyrimeth.</td>
<td>auto</td>
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<td>1977</td>
<td>47/M</td>
<td>15 days</td>
<td>hemiparesis, dementia</td>
<td>transpl. rejection, pneumonia, abscesses, cardiac ins.</td>
<td>Azathioprine, Prednisone, Methylpred</td>
<td>L-8</td>
<td>P-112</td>
<td>1/3200 Pyrimeth.</td>
<td>1/2048</td>
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<td>1979</td>
<td>40/F</td>
<td>2 years</td>
<td>headaches, psychosis</td>
<td>uveitis</td>
<td>Azathioprine, Prednisone, Methylpred</td>
<td>Immunophyl.</td>
<td>Trisulph.</td>
<td>1/128</td>
<td></td>
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<td>1980</td>
<td>18/F</td>
<td>28 days</td>
<td>hemiparesis, blindness, III &amp; VII pair</td>
<td>uveitis</td>
<td>Azathioprine, Prednisone, Methylpred</td>
<td>Immunophyl.</td>
<td>Sulphadine</td>
<td>1/128</td>
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<td>1980</td>
<td>31/M</td>
<td>6 years</td>
<td>hemiparesis, blindness, III &amp; VII pair</td>
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<td>Azathioprine, Prednisone, Methylpred</td>
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<td>Sulphadine</td>
<td>1/128</td>
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<td>1982</td>
<td>?</td>
<td>28 days</td>
<td>disorient, myoclonus</td>
<td>graft rejection, uraemia, pneumonia</td>
<td>Azathioprine, Prednisone, Methylpred, IAT</td>
<td>Immunophyl.</td>
<td>1/128</td>
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<td>1983</td>
<td>30/F</td>
<td>21 days</td>
<td>fever, convulsions, coma</td>
<td>graft rejection, pneumonia</td>
<td>Azathioprine, Prednisone, Methylpred, (myocard, enceph. pneum. adren.)</td>
<td>Immunophyl.</td>
<td>1/128</td>
<td></td>
<td></td>
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<tr>
<td>1986</td>
<td>30/M</td>
<td>28 days</td>
<td>fever, headaches</td>
<td>graft rejection, hepatitis, myositis</td>
<td>Azathioprine, Prednisone, Methylpred, (ventric. dilat.)</td>
<td>Immunophyl.</td>
<td>IgG 1/1024</td>
<td></td>
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<td>1985</td>
<td>19/M</td>
<td>14 days</td>
<td>fever, convulsions, obtinub. fever, convulsions</td>
<td>pneumonia, acute tubular necrosis, myositis, pericarditis</td>
<td>Azathioprine, Prednisolone, Methylpred, Cyclosporine</td>
<td>CAT (normal)</td>
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<td>1987</td>
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<td>fever, convulsions</td>
<td>pneumonia, acute tubular necrosis, myositis, pericarditis</td>
<td>Azathioprine, Prednisolone, Methylpred, Cyclosporine</td>
<td>CAT (normal)</td>
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Saraiva Da Cunha, et al. 2022. Table 2 - Summarized description of the published cases of Cerebral Toxoplasmosis in subjects with renal transplants.
The study of cerebrospinal fluid (CSF) was made in twelve patients and their characteristics were normal in 4 (33%) of them. When altered, it implies a slight increase in cells (predominantly mononuclear) and proteins; the quantification of the intratecal production of antitoxoplasma antibodies is a controversial subject, since if it does not seem to have great diagnostic use for some 35, there are others who state that it has some value with patients infected by HIV 36. The analysis of CSF is fundamentally to exclude other causes of opportunistic infection of the CNS which may develop with similar clinical and radiologic features, such as listeriosis, tuberculosis or cryptococcosis.

CT is invariably fatal in the absence of treatment, there being only one case in which the patient survived 18. If treatment is begun in time, it is sufficiently effective, since only in one case (the first in which it was used) did the patient die 20. The preconized scheme consists of the association of sulfadiazine (4 to 6g per day, every 6 hours) with pyrimethamine (50-75mg per day) for 4 to 6 weeks; to avoid medullar toxicity of pyrimethamine, folic acid should also be associated (10-15mg per day), although its efficacy has not yet been proved definitively 4. In view of the high toxicity of this treatment (which may occur in approximately 50% of the patients), it is important to find alternatives which are better tolerated, but also effective; clindamycin, new macrolides (particularly azithromycin) 7 and atovaquone (566C80) 37 fit into this group.

The treatment of CT is not active against the cystic forms of the parasite, therefore secondary prophylaxis is justified in patients in which the mechanisms of cellular immunosuppression persist; the same antinmucobis may be chosen, but in lower daily doses (sulfadiazine - 2g; pyrimethamine - 25mg), or also dapsone or clindamycn to replace sulfadiazine 47.

In view of the fact that sulphamides are implicated in the occurrence of allergic vasculitis of the kidney and

<table>
<thead>
<tr>
<th>Year</th>
<th>Case No</th>
<th>Gender</th>
<th>Age</th>
<th>Onset</th>
<th>Diagnosis</th>
<th>EEG (temporal)</th>
<th>IgM 1/8192</th>
<th>Pyrimeth. dye test</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988°F</td>
<td>7 years</td>
<td>Hodgkin’s disease</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>deceased autoppy (cerebral toxoplasmosis)</td>
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<td>1991 (b,d)</td>
<td>58/M</td>
<td>42 days</td>
<td>fever</td>
<td>mental confusion</td>
<td>pneumonia</td>
<td>Azathioprine</td>
<td>CAT (normal)</td>
<td>L-13</td>
<td>ELISA IgG 500 U IgM neg.</td>
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<tr>
<td>1991 (b,d)</td>
<td>15/F</td>
<td>14 days</td>
<td>fever</td>
<td>convuls.</td>
<td>pneumonia</td>
<td>Azathioprine</td>
<td>Prednisolone</td>
<td>CD3</td>
<td>L-28</td>
</tr>
<tr>
<td>1991 (b,d)</td>
<td>14/M</td>
<td>7 days</td>
<td>fever</td>
<td>headaches</td>
<td>pneumonia</td>
<td>Azathioprine</td>
<td>Prednisolone</td>
<td>Muromonab</td>
<td>CD2</td>
</tr>
</tbody>
</table>

ref. - bibliographic reference; & ALG - antilymphocytic globulin; ATG - antithymocyte globulin; "L" - lymphocytes/mm3; N - neutrophils/mm3; C - cells/mm3; P - proteins (mg/dl); G - glucose (mg/dl); NOTE: highest values reached; 17 only the main organs with evidence of Toxoplasma infection indicated; E two predisposing situations co-exist in this case; § hepatic and renal transplant; (a) proven forms of reactivation; (b) proven forms transmitted by the donor; (c) isolation of Toxoplasma gondii in the blood; (d) isolation of Toxoplasma gondii in alveolar lavage.

The symptomatology was also very diverse, observing that the presence of fever, headaches, convulsions, focal neurological signs or alterations in awareness in immunocompromised patients are a warning of an eventual CNS infection 34. The graft was rejected in 6 patients (29%), it being very difficult to prove if it was as a result of infection by Toxoplasma; it may even happen that, on the contrary, this occurs in consequence of the aggressive immunosuppression to which many of these patients with episodes of rejection are subjected 32.

Serologic and imaging studies contribute decisively to the confirmation of CT diagnosis.

The various serologic techniques available may confuse the interpretation of the results, more facilitated today by the general recourse to automatic immunoenzymatic and immunofluorescent methods 3. The search for antibodies against Toxoplasma gondii, when made in peripheral blood, was universally positive, confirming the notion that the possibility of it being negative places serious reservations as to the diagnosis of CT; however, a seroconversion or a positive IgM in these immunocompromised patients rarely occurs, it being more frequent during the course of an acute infection propagated by the transplanted organ 4. Just as it happens with our patient (Table 1), there may still be temporal variations in antibody titres without any clinical explanation 4.

The remarkable technological progress made in the field of neuroradiology allows more precise and earlier diagnosis of CT, particularly in its focal form. The images shown by CAT or by MRI of the cranium are sometimes very suggestive (although not pathognomonic) of infection by Toxoplasma gondii 4. Curiously, of the 8 patients in which the use of a CAT was referred, it was normal in four (50%), confirming the notion that the encephalitic form predominates in these patients.

Electroencephalograms were regularly performed and showed an invariably altered pattern, although without any diagnostic specificity.

S 65
obstructive uropathy second to cristaillaria, particularly with high doses of sulphadiazine employed in the treatment of CT 30, we decided to prescribe clindamycin to our patient, since a recent study of patients with AIDS showed the same efficacy of the clindamycin- pyrimethamine association in comparison with the classic scheme 39. The patient we followed was the first known case of successful treatment of CT in a renal transplant subject, through clindamycin-pyrimethamine association.

The anamato-pathological tests on the 14 deceased patients show that infection by Toxoplasma gondii was rarely confined to the CNS, the disseminated forms being common, with pulmonary, cardiac and muscular involvement.

In future we hope that more diagnostic methods for infection by Toxoplasma, such as the observation of tachyzoites in the broncho-alveolar lavage 30, tissue culture 40, or mainly the research of its genetic material 41, may simplify the clinical approach to these patients. In cases of doubt or insufficient response to treatment, it may be justifiable to perform a cerebral biopsy, although it is an examination which is not free of some risks.

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