

# Cerebral toxoplasmosis after haematopoietic stem cell transplantation

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## Abstract

Toxoplasmosis is an opportunistic infection caused by the parasite *Toxoplasma gondii*. The infection is severe and difficult to diagnose in patients receiving allogeneic haematopoietic stem cell transplantation (HSCT). It frequently involves the central nervous system. The case is presented of cerebral toxoplasmosis in a 17-year-old youth with Fanconi anaemia treated with haematopoietic stem cell transplantation (HSCT).

## Key words

toxoplasmosis, Fanconi anaemia, haematopoietic stem cell transplantation

## INTRODUCTION

Toxoplasmosis is an opportunistic infection caused by a parasite *Toxoplasma gondii*. Infection in an immunocompetent host leads to latency of the parasite as cysts in various organs. Severe infection occurs in highly immunocompromised patients, mostly by reactivation of latent cysts, but also as a primary infection [1, 2]. Toxoplasmosis in patients following haematopoietic stem cell transplantation (HSCT) is a rare, but life-threatening infection, with a high mortality rate [3]. It frequently involves the central nervous system, both as an isolated cerebral infection, or in a disseminated disease [1, 2, 4]. It may also affect intellectual abilities in some patients. The case is presented of cerebral toxoplasmosis, diagnosed in the post-transplant period in a youth with Fanconi Anaemia (FA), transplanted from a matched unrelated donor.

**Demographical data.** A 17-year-old youth was diagnosed as having Fanconi Anemia (FA) in adolescence, at the age of 15 years. The youth was living in a rural area, with an older healthy brother, both parents and grandmother. During treatment, the patient's family received psychosocial support from family members and friends. The socio-economical status of patient's family was good. The parents had a high level of education, but the patient had school difficulties before treatment. There was no data on toxoplasmosis infections in the other family members.

**HSCT status.** Six months after diagnosis of FA, the patient underwent allogeneic HSCT from a 10/10 matched, unrelated donor. Pre-transplant conditioning included cyclophosphamide (50 mg/kg/day for 4 consecutive days) and fludarabine (35 mg/m<sup>2</sup> of body surface area/day for 5 consecutive days). Antithymocyte globuline and cyclosporine with short-term methotrexate were administered for Graft versus Host Disease (GvHD) prophylaxis. The pre-transplant *Toxoplasma gondii* serostatus of the recipient was unknown, the donor was toxo-seronegative, pre-transplant

Cytomegalovirus (CMV) serostatus of the donor and recipient were positive. The early post-transplant period proceeded without complications, except for staphylococcal bacteraemia and infection diagnosed on day 4, which resolved after antibiotic therapy. Engraftment of leucocytes as well as granulocytes were noted on day 12 post-transplant. Complete donor chimerism with PCR method was found on day 10 and maintained until now. Acute graft versus host disease (aGvHD) was not observed. The patient was discharged from hospital on day 30 post-transplant. A week later, every evening, fever episodes started. Diagnostic procedures towards infections, including imaging studies, e.g. abdominal ultrasonography as well as thoracic and abdominal computer tomography (CT), were negative. As well as C-reactive protein, bacteriology and viral tests, except for positive Epstein-Barr virus (EBV) PCR test. EBV reactivation resolved after 2 weeks of preemptive treatment with rituximab. GvHD prophylaxis was discontinued at day 120. Three months post-transplant, visual impairment occurred. Changes on the retina during eye examination: macular oedema, retinochoroidal scars were found, and chorioretinitis of the right eye was diagnosed. Toxoplasmosis serology test by the chemiluminescence method was negative in IgM (<0.9 IU/ul), and positive in IgG (37.7 IU/ml) at that time. Tests are considered positive when IgG or IgM titers exceed 10 IU/ml. According to the clinical signs of ocular infection, anti-toxoplasma treatment with clindamycin and trimetoprim was started. After 2 weeks of combined treatment no clinical improvement was obtained, visual impairment maintained and chronic fever episodes were observed. At the same time, toxo serology became strongly positive (IgM 1100 IU/ul and IgG 14.43 IU/ml), and persisted for next 2 months despite continuing treatment (Tab. 1).

**Neurologic status.** Six months post-transplant, the youth was found at home with consciousness disorders, periodically without logical contact, with symptoms of sensory aphasia. On admission to hospital, the patient complained of headache, malaise, discomfort, myalgias, abdominal and inguinal pain and chronic fever. Toxo-serology was still positive (IgM -15.70 IU/ml and IgG -242 IU/ml). Cerebral computer tomography (CT) and magnetic resonance imaging (MRI) scans showed

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**Table 1.** Results of serology tests for toxoplasmosis in postransplant period

Month postransplant	Toxo IgG [IU/ml]*	Toxo IgM [IU/ml]*
3	37.7	<0.9
4	1100	14.43
6	242	15.7
12	>700	7.85
18	>700	1.41
24	>700	1.13

\*Toxo IgG, IgM values range: negative < 6.4 IU/ml; doubtful 6.4 – 9.9 IU/ml; positive > 10.0 IU/ml

multifocal calcifications in left and right occipital lobes, in the frontal lobe, in temporal lobes and in the left parietal lobe. The biggest calcification was located subcortical in frontal lobe with an accompanying zone of increased signal (cytotoxic oedema susp.). Such images are seen not only in cerebral reactivation of toxoplasmosis, but also in cryptococcosis and aspergillosis. Electroencephalography (EEG) recording was incorrect with localized changes. In cerebrospinal fluid (CSF), pleocytosis (47/ul) with limfocytosis (95%) was found, protein was raised and Pandy reaction positive. Toxo-serology in CSF was also positive (IgM 0.65 IU/ml, IgG 21 IU/ml). The serological method used for diagnosis of toxoplasmosis in the presented case is the chemiluminescence method, with the following values range: negative < 6.4 IU/ml, doubtful 6.4–9.9 IU/ml, positive > 10.0 IU/ml. Toxo-PCR tests were negative, both in CSF and in the blood, as well as other PCR tests for CMV, EBV and cryptococcus. For diagnosis, PCR Real-Time qualitative method was used.

Intensive antiprotozoal treatment with high doses of trimetoprim and dexamethasone was introduced and continued for 6 months. Clinical status gradually improved, neurological symptoms resolved, as well as MRI symptoms, but toxoplasma serology tests remained highly positive, especially in IgG. The results of serology test for toxoplasmosis in post-transplant period are shown in Table 1. The patient is now in a good clinical condition, his neurological status is normal, changes in the eye resolved completely, leaving changes typical for ocular toxoplasmosis cicatrice.

**Psychological status.** From the beginning of hospitalization, the patient was under planned psychological and psychosocial care. Both intelligence quotient (IQ) and quality of life (QL) were examined before and after HSCT procedure, according to the established model of care [5]. Quality of life level was additionally examined 6 months post-transplant, due to toxoplasmosis infection. Respectively, Wechsler's scales (WISC-R and WAIS-R PL) as measure of intelligence, and The Short Form (36) Health (SF-36) as a measure of health status, were used. Additionally, psychosocial adaptation of the patient's family was checked using the PAT 2.0 questionnaire [6]. The level of the youth's pre-transplant general intellectual ability (Full Scale IQ) was average (FSIQ=91), with significant imparity between Verbal IQ (VIQ=100) and Performance IQ (PIQ=83). In post-transplant IQ scores, a small increase was observed in FSIQ, PIQ, and VIQ levels, sustaining the same tendency. Low scores in the Performance Scale subtests may have an organic basis due to the long-standing periods of anaemia. In the quality of life measurement, high scores were stated 6 months post-transplant, after toxoplasmosis infection. In the Polish

Version of the SF-36 Questionnaire, the higher the score the more disability in the patient's health status. Detailed patient's intelligence and quality of life characteristics in different treatment stages are presented in Table 2.

**Table 2.** Patient's intelligence and quality of life characteristics in different treatment stages

Treatment stage	Intelligence			Quality of life		
	FSIQ	VIQ	PIQ	Health status	Physical Health	Mental Health
pretransplant	91	100	83	18	2	2
6 months posttransplant				105	30	39
24 months posttransplant	103	113	90	23	1	2

FSIQ – Full Scale Intelligence Quotient

VIQ – Verbal Intelligence Quotient

PIQ – Performance Intelligence Quotient

IQ ranges in Wechsler's Scales: Low Average [80–89]; Average [90–110]; High Average [110–119]

## DISCUSSION

Fanconi Anaemia is autosomal recessive or X-linked congenital disease, characterized by progressive bone marrow failure, developmental defects, predisposition to malignancy and different alterations in immunologic function (impairment of T-cell function, NK and macrophage function [7, 8]. Haematopoietic stem cell transplantation may be associated with several complications, including neurologic, which may be secondary to the treatment toxicity, prolonged immunosuppression or an underlying disease. Common neurologic complications are infections, including toxoplasmosis. Recent studies showed that toxoplasma disease may develop from 0.25–4% allotransplant recipients, with a mortality rate as high as 60–90% [3, 4, 9, 10, 11, 12, 13]. PCR techniques have been developed for noninvasive diagnosis, also in cerebral toxoplasmosis, which contribute to rapid diagnosis and monitoring of treatment efficacy [1, 2, 9, 10, 11, 13, 14, 15, 16]. Some authors, however, still emphasize the role of serology in the diagnostics of toxoplasmosis, as well as a combination of serology and PCR techniques [9,11]. Serological tests are very useful before transplantation to assess serostatus of the recipient and donor, and for monitoring the recipient after transplantation [11, 13].

The question remains, why PCR test, which seemed to be very useful in the diagnosis of disseminated toxoplasmosis, as well as in cerebral toxoplasmosis, was negative in the presented case. Radiologic methods as non-invasive MRI where typical findings, such as multiple, ring-enhancing brain lesions often associated with oedema, may facilitate or confirm the diagnosis in the context of serological or PCR tests. However other infections, such as aspergillosis and cryptococcosis, may cause similar lesions; therefore, combined diagnostic tools need to be used to enable correct diagnosis and to start proper treatment. The patient in the presented had probable cerebral toxoplasma disease, diagnosed according to clinical symptoms preceded by retinochorioiditis, radiologic evidence of brain involvement and positive toxo-serology from CNF in the acute phase of the disease, but not with the PCR tests which were negative, both from the blood and CSF. Good response for anti-toxo therapy may confirm the diagnosis. The good result of the treatment may also be due to the recovery of the immune system (CD4>100/ul during the first month of the treatment).

Fanconi anaemia is commonly associated with a range of neurological and developmental issues characterized by mild to significant impairment, such as attention deficit, hyperactivity disorder (ADHD), learning disabilities, and developmental delay [18, 19]. In the current case, only mild learning difficulties and periodic decrease in quality of life were observed due to cerebral toxoplasmosis. However, any young person (child or youth) with FA and learning disabilities, especially after HSCT procedure, should be monitoring for psychosocial functioning.

## CONCLUSIONS

The toxoplasmosis status should be monitored in patients treated with HSCT, especially in seropositive recipients transplanted from seronegative donors, to introduce pre-emptive therapy which may help to reduce the risk of developing disseminated or cerebral disease. The principle of pre-emptive therapy is to prevent development of the disease, not to prevent infection, in very high risk patients. This is particularly important early post-transplant when patients are highly immunocompromised.

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