

Long term ocular and neurological involvement in severe congenital toxoplasmosis

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Abstract

Aims—This study was set up to determine the long term ocular and systemic sequelae in patients with severe congenital toxoplasmosis.

Methods—Cross sectional and retrospective study of 17 patients with severe congenital toxoplasmosis.

Results—In addition to chorioretinitis (100%), the most common abnormal ocular features were optic nerve atrophy (83%), visual acuity of less than 0.1 (85%), strabismus, and microphthalmos. In 50% of cases we observed iridic abnormalities and about 40% developed a cataract. Overt endocrinological disease, diagnosed in five of 15 patients, included panhypopituitarism (n=2), gonadal failure with dwarfism (n=1), precocious puberty with dwarfism and thyroid deficiency (n=1), and diabetes mellitus and thyroid deficiency (n=1). The observed endocrinological involvement was associated in all cases with obstructive hydrocephalus with a dilated third ventricle and optic nerve atrophy.

Conclusion—The recognition of long term ocular, neurological, and endocrinological sequelae of congenital toxoplasmosis is important for medical management of these severely handicapped patients.

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involvement in adolescent and adult patients with severe congenital toxoplasmosis.

Patients and methods

We reviewed the complete clinical data (ophthalmic, neurological paediatric, psychological, and medical) on 17 patients with severe congenital toxoplasmosis, all residents of 'Bartimeushage' in Doorn, an institute for visually and mentally handicapped children and adults. The cases represent all patients suffering from congenital toxoplasmosis who resided in Bartimeushage over a period of past 10 years. Medical records covered the period from birth until the present study; mean follow up was 27 years. The male/female ratio was 11/6, and the mean age was 27 years (range 17-37). Two of the patients died at the age of 22 years (cause of death aspiration pneumonia and pyelonephritis with pneumonia). Complete examinations of the surviving 15 patients were performed by an ophthalmologist, neurologist, and internist.

The diagnosis of congenital toxoplasmosis was performed within the first year of life in all cases. The diagnosis was performed more than 25 years ago and the criteria are not up to the recent standard; many laboratory examinations we use now were not available at that time. The diagnosis of congenital toxoplasmosis was based on documented seroconversion of the mothers during pregnancy (three patients) and positive antitoxoplasmic titres persisting for more than 1 year in the neonates (additional 13 patients). For one patient the diagnosis of congenital toxoplasmosis was based on the clinical presentation (hydrocephalus with multiple intracerebral calcifications, psychomotor retardation, epilepsy, and bilateral necrotising chorioretinitis); information on the antitoxoplasmic titre of the mother and during the child's postnatal period was not available.

IgM and IgA levels were not assessed since these tests were not available at that time. The patients underwent clinical, serological, and x ray examinations (which were appropriate at that time) for the presence of syphilis, tuberculosis, rubella, and other possible causes of the neurological and ocular diseases; however, the results of these tests were not contributory. Nine patients were treated postnatally with pyrimethamine and sulphadiazine. Owing to the occurrence of severe side effects, two were switched to rovamycin therapy. The duration of treatment varied between 2 and 10 months.

Congenital toxoplasmosis constitutes a serious health hazard and preventive measures are continuously being recommended.¹ The broad clinical spectrum of congenital toxoplasmosis ranges from stillbirth or death shortly after birth to survival with either cerebral damage or mild or subclinical disease, consisting usually of ocular involvement.^{2,3} Long term follow up has shown that 80% of the subclinically infected children develop ocular sequelae later in life.⁴

The hallmark of congenital ocular toxoplasmosis is focal necrotising chorioretinitis, which may be present at birth but in most patients becomes manifest during adolescence.⁴⁻⁶ In addition to recurrent focal chorioretinitis, various other ocular symptoms (for example, microphthalmos, juvenile cataract, and strabismus) have been reported.⁷

Most studies on ocular involvement in congenital toxoplasmosis deal with subclinical or mild disease.⁴⁻⁶ The aim of this study was to determine the extent of ocular and systemic

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Table 1 Ocular findings for 17 patients with severe congenital toxoplasmosis

	No of eyes (%)
Visual acuity <0.3	27/34 (79)
Microphthalmos (horizontal cornea diameter <10 mm)	18/34 (53)
Degenerative corneal changes	13/34 (38)
Iridic involvement (atrophy, translucency, heterochromia)	16/34 (47)
Juvenile cataract	13/32 (42)
Chorioretinitis scars	33/34 (97)
Optic nerve atrophy	24/29 (83)

The diagnosis of severe congenital toxoplasmosis was defined as the combination of psychomotor retardation, epilepsy and focal necrotising retinitis due to congenital toxoplasmosis.² All patients fulfilled the three above mentioned criteria.

The intracerebral calcifications were present in 12 cases. Obstructive hydrocephalus was diagnosed in the first months of life in 10 cases; all patients were treated and all required repeated shunting procedures. The cranial computed tomography (CT) scans of 15 patients were re-evaluated and compared with those of a control group in a masked study. The CT scans of the two deceased patients were not available and these patients were therefore excluded from neurological re-evaluation. The control group for CT scanning consisted of 15 individuals suffering from cortical visual impairment and various neurological symptoms due to a cerebral palsy syndrome of perinatal origin.

The complete ophthalmic examination of all surviving patients included: visual acuity test, slit-lamp examination, and indirect funduscopy. For patients with severe mental retardation preferential looking tests and pattern visual evoked responses were performed. Anterior segment photographs were taken whenever the cooperation of the patient allowed.

Diagnosis of ocular toxoplasmosis was based on the clinical picture: all 17 patients had the typical toxoplasmic chorioretinitis: a focal necrotising retinitis resulting in atrophic scars.⁸ All patients were positive for antitoxoplasmic IgG antibodies.

Since the axial length measurements were not available, the diagnosis of microphthalmos was based on a horizontal corneal diameter of less than 10 mm. Although the presence of an isolated microcornea (without microphthalmos) cannot be definitively excluded, this abnormality is rare and not probable in our patients.

Results

OPHTHALMIC INVOLVEMENT

Ocular findings for the patients are shown in Table 1. Visual acuity of more than 0.3 was found for 1/34 eyes (3%), visual acuity between 0.1 and 0.3 for four eyes (12%), and less than 0.1 for 29/34 eyes (85%). There were 12 patients with bilateral visual acuity of less than 0.1; five patients had unilateral acuity of more than 0.1. Strabismus was observed in 13/17 (76%) patients.

Microphthalmos was present in 18/34

(53%) eyes (10 individuals) and was of congenital origin in all cases. Degenerative corneal changes (band keratopathy and sclerocornea) were observed in 13/34 (38%) eyes. Band keratopathy manifested at the mean age of 18 (range 5–30) years. A shallow anterior chamber (due to swelling of the lens) was observed in 13/34 (38%) eyes. In one patient acute narrow angle glaucoma became manifest at the age of 27 years.

Heterochromia of the iris was observed in three patients (18%); and developed at 8, 13, and 27 years of age. Iridic atrophy associated with translucency was observed in 16/32 (50%) eyes (in two eyes the iris could not be examined in detail as a result of band keratopathy in one case and extreme microphthalmos in the other). The majority of the cases with iris atrophy were manifested in children between the ages of 5 and 10 years. Of these 16 eyes (eight patients) with iridic atrophy, 12 (75%) also exhibited atrophic changes in the eyeball and four (25%) were eyes of normal size without associated atrophic features. Synechiae in the posterior and anterior iris were observed in five patients; one additional patient had a iridic cyst.

Cataracts were present in 13/32 (42%) eyes (nine individuals; in two eyes the lenses could not be visualised because of band keratopathy in one case and extreme microphthalmos in the other). Of those, three were congenital, five manifested within the first decade of life, and five presented at older age.

All patients had the typical toxoplasmic retinal scars, unilateral in one case and bilateral in 16 cases (33/34 eyes, 97%). Recent funduscopy of five eyes was impossible because of band keratopathy, extreme microphthalmos, cataract, and/or lack of cooperation of the patient; however, toxoplasmic scars were documented in all of the above mentioned cases during earlier stages of the disease. Recurrence of toxoplasmic retinitis was documented in 3/17 (9%) patients (three eyes). Of those three, one patient had received prolonged antiparasitic treatment during the first 10 months of life, the two others had not. Optic nerve atrophy was found in 24/29 (83%) eyes (13 individuals). Retinal detachment occurred in two of the patients with severe congenital toxoplasmosis.

SYSTEMIC INVOLVEMENT

Obstructive hydrocephalus with enlargement of the third ventricle was found in 10 of 15 patients with toxoplasmosis and none of the controls with a cerebral palsy syndrome of perinatal origin. Obstructive hydrocephalus was absent in two patients while CT scans were not available in three cases.

Overt endocrinological disease, diagnosed in five of the 15 cases of severe congenital toxoplasmosis, included panhypopituitarism (two patients), gonadal failure with dwarfism (one patient), precocious puberty with dwarfism and thyroid deficiency (one patient), and diabetes mellitus and thyroid deficiency (one patient). The full blown endocrinological

disease manifested at the mean age of 12 (range 9–16) years; however, in two patients isolated hormone deficiency started several years earlier. In two additional patients possible endocrinological disease was noted (one patient suffered from severe adiposity and a low normal thyroid function, another had an abnormal glucose tolerance test and a low normal thyroid function). Furthermore, three patients with toxoplasmosis (including two with endocrinological disease) suffered periodically from severe hypothermia, requiring admission to the intensive care unit. Three patients (including two with endocrinological disease) had cardiovascular abnormalities. In addition, temporary mental disorders, such as periods of aggressive behaviour, were exhibited by five of the 15 patients. The observed endocrinological involvement was associated with obstructive hydrocephalus and a dilated third ventricle together with optic nerve atrophy in all of these cases.

Discussion

In addition to chorioretinitis the most common abnormal ocular features in patients with severe congenital toxoplasmosis were optic nerve atrophy (83%), visual acuity of less than 0.1 (85%), strabismus (76%), and microphthalmos (53%). One half of the patients exhibited iridic abnormalities and about 40% developed a cataract.

The frequent finding of optic nerve atrophy in patients with congenital toxoplasmosis could be explained by either hydrocephalic dilatation of the third ventricle or an inflammatory toxoplasmic infiltrate. In the majority of the cases (20/28) severe visual impairment was associated with optic nerve atrophy.

The documented recurrence of retinitis in 9% of our patients is markedly lower than the recurrence rate reported for patients suffering solely from ocular involvement.⁸ One may hypothesise that this low recurrence rate may be due to the stronger and/or longer lasting immunity caused by severe generalised infection in our patients. In five eyes funduscopy became impossible and the eventual recurrences in these eyes cannot be ruled out. Another explanation could be that the patients with psychomotor retardation do not report their ocular complaints promptly. However, this phenomenon seems unlikely, since the retinal lesions of all patients were carefully documented either by photographs or drawings; during follow up no changes were recorded. The treatment in the postnatal period did not seem to influence the recurrence rate (one recurrence in two patients who received the antiparasitic treatment for longer than 6 months). However, to draw general conclusions is impossible since the numbers of patients are too small.

Iridic abnormalities in patients with toxoplasmosis may be due to inflammation caused by *Toxoplasma gondii* located in the iris or may represent a specific secondary atrophy. Since 25% of the eyes with atrophy of the iris exhibited no evidence of other associated

atrophic features, it is possible that *T gondii* is directly involved in the pathogenesis of the observed iridic abnormalities. Involvement of the iris without retinal disease has been described in an AIDS patient with toxoplasmosis.⁹ The histopathological findings for this patient showed several toxoplasmic cysts in the stroma of the iris. Furthermore, an association between ocular toxoplasmosis and Fuchs' heterochromic cyclitis, a disease associated with extensive iridic atrophy, has also been reported.^{10–12} However, biopsies of the iris and analysis of intraocular fluids from patients with heterochromic cyclitis do not indicate that *T gondii* is involved in the pathogenesis of iridic changes.¹³ Histological examination of the iris of patients with severe congenital toxoplasmosis could answer the question of whether the changes in the iris observed in 50% of our patients are caused by the parasite itself or represent a secondary response to 'overspill' of an iridic inflammation.

The endocrinological disease is most probably due to damage in the hypothalamic area, caused by either hydrocephalic dilatation of the third ventricle and/or an inflammatory toxoplasmic infiltrate. The endocrine abnormalities in our patients were in all cases associated with obstructive hydrocephalus. Furthermore, the CT scans did not show any focal inflammatory lesions or calcifications in the hypothalamic area. Yet, with this technique the presence of microlesions cannot be excluded and therefore inflammatory lesions cannot be ruled out definitely as a cause of endocrine involvement.

The association of hydrocephalus with endocrinological disease has previously been reported.¹⁴ A case of pituitary dwarfism in a male with congenital toxoplasmosis was attributed to pituitary or hypothalamic disease.¹⁵ The abnormal temperature regulation, cardiovascular disease and severe behavioural disturbances observed in our patients may be explained by non-endocrine manifestations of hypothalamic damage.

We found evident endocrinological disease, probably due to hypothalamic dysfunction, in one third of patients with severe congenital toxoplasmosis. All had optic nerve atrophy associated with poor visual acuity. Since some of the endocrinological symptoms may be hidden by or even confused with signs of psychomotor retardation, we wish to emphasise the fact that correct diagnosis and eventual treatment of endocrinological disease may benefit these severely handicapped patients.

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