Neurological toxoplasmosis presenting as a brain tumor

Case report

FRANCESCO TOGNETTI, M.D., ERCOLE GALASSI, M.D., AND GIULIO GAIST, M.D.

Divisions of Neurosurgery, Bellaria Hospital, Bologna, Italy

A case of congenital toxoplasmic mass lesion is reported in an infant born to a mother who acquired Toxoplasma infection during her pregnancy. Radical surgery followed by chemotherapy appeared to be curative. Previously described cases of acquired and congenital mass lesions due to Toxoplasma infection are summarized. The possible delayed onset and the misleading features that congenital toxoplasmosis may display are stressed.

KEY WORDS • intracranial tumor • microglial nodule • antibodies • subclinical infection • toxoplasmosis

CONGENITAL Toxoplasma infection of the central nervous system (CNS) has previously been considered only in infants with the “classical triad” of hydrocephalus, chorioretinitis, and intracranial calcifications. It is now well established that congenital toxoplasmosis exhibits several patterns. The clinical spectrum at birth may range from a normal appearance to severe and diffuse cerebral damage. Signs of an intracranial space-occupying lesion in an infant with subclinical or overt toxoplasmosis are easily misdiagnosed because of the rarity of this toxoplasmic pattern. Moreover, if the physician is not aware of the underlying condition, the infant can be incorrectly regarded as harboring a primary cerebral tumor.

We report a patient with unrecognized congenital toxoplasmosis who, beginning at 1 year of age, had delayed psychomotor development. The true neurological signs were detected some months later.

Case Report

This 19-month-old baby girl was born postterm (at 42 weeks gestation) after a normal pregnancy and delivery. The body weight at birth was 3350 gm, the length 51 cm, and head circumference 34 cm. Developmental milestones were normal until the patient was 1 year of age, when subtle but progressive mental and behavioral changes commenced. She became increasingly restless, and cried frequently. She was often obtunded but could always be aroused during the day. Her periods of sleep became irregular. Within a few weeks, she could not sit unsupported or walk without assistance.

A few months later, the child exhibited a progressive increase in head circumference, with bossing on the right side. Computerized tomography (CT) performed elsewhere showed a cystic mass occupying the whole right cerebral hemisphere (Fig. 1). The patient was transferred to our institution on August 30, 1980, with a presumptive diagnosis of cystic astrocytoma.

Examination. She was an alert but uncooperative child. The skull circumference was 56 cm (over the 97th percentile), and there was a gross temporoparietal prominence on the right side. The anterior fontanel was enlarged (4 × 4 cm), soft, and bulging. The coronal and sagittal sutures were slightly separated.

Nystagmus was present on lateral gaze, but the fundi showed no abnormalities. Skeletal muscle tone was asymmetrically increased (more on the left), with left hemiparesis, diffuse hyperreflexia, and bilateral upgoing toe reflexes. A gross tremor affected all movements. When sitting, the patient showed head and truncal titubation, with a tendency to deviate to the right. On standing, unsteadiness was immediately evident.
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Laboratory studies revealed a white blood cell count of 14,700/cu mm, with 82% lymphocytes. Hemoglobin, hematocrit, blood chemistry, urinalysis, electrocardiogram, and chest x-ray films were within normal limits. A skull series showed wide fontanels, split sutures, and bulging of the right cranial vault, with marked thinning of the cortical bone. Carotid angiography was consistent with a right frontotemporal avascular mass lesion (Fig. 2).

Operation. A wide right frontal craniotomy was performed on October 1, 1980. The bone was paper-thin. The dura was tense, and after it was incised, the brain bulged out. The frontotemporal cortical surface appeared translucent, and only a few millimeters thick. It was incised along the superior temporal region, revealing a huge cavity containing clear but highly xanthochromic fluid under elevated pressure. The isolated right temporal horn lay in the anterior part of the cavity. The medial wall of the cyst was explored and the foramen of Monro was not found.

Under the anteromedial ependyma, a hard grayish mural nodule, 3 cm in size, bulged out. There was a good plane of cleavage, and the lesion could be removed en masse. A communication was then fashioned between the lateral ventricles by incising the septum in an avascular zone.

Pathological Examination. Microscopic examination showed the mass to be chiefly microglial in nature. Rare toxoplasmic pseudocysts, the residual form of the parasite, were discovered within the nodule (Fig. 3 left). Perivascular infiltrates of polymorphonuclear and mononuclear cells and small mil- liary calcifications (psammomatous bodies) were also present (Fig. 3 right). The cyst fluid contained high levels of albumin (11.5 gm/liter) and globulins (Pandy, Nonne-Appelt, and Weichbrodt tests all strongly positive), with 2 to 3 cells/cu mm. No growth

Fig. 1. Computerized tomography scan after injection of contrast material showing a huge cyst occupying the entire right cerebral hemisphere. A marked midline shift to the left and a moderate enlargement of the left ventricle are present.

Fig. 2. Right carotid angiography, lateral (left) and anteroposterior (right) views, showing anterior displacement (left) with shift of both anterior cerebral arteries to the left side (right). Elevation of the middle cerebral artery with medial displacement of the Sylvian group can be seen (right).
was obtained on culture, but an indirect fluorescent antibody (IFA) test proved slightly positive in the detection of specific anti-Toxoplasma gamma globulins. Both the dye and the IFA tests performed on the patient's serum exhibited low positive reactions, with a titer of 1:256 and 1:128, respectively.

In view of the histological and laboratory data, a careful retrospective analysis of the mother's gestation was carried out, and revealed a febrile lymphonodular illness during the 2nd month. Serological tests had failed to detect rubella antibodies, but testing for Toxoplasma had not been performed.

In light of the daughter's findings, the mother underwent tests for Toxoplasma in our hospital. Maternal dye and IFA test titers were 1:64 and 1:128, respectively, revealing signs of an old infection.

Postoperative Course. The first 24 hours after surgery were uneventful. On the 2nd day, however, the child experienced 30- to 40-second partial seizures, with right facial muscle involvement. A course of clonazepam was promptly started (0.625 mg twice a day).

The patient was discharged 20 days postoperatively on a course of pyrimethamine and sulfadiazine to control the Toxoplasma infection, and clonazepam for control of seizures. She was reevaluated 8 months later, at which time she was free from tremor and unsteadiness, and was able to stand and walk unsupported.

She exhibited only slight bulging of the right side of the head, and had a small (2 × 2 cm) anterior fontanel. Mentation and sleep were normal, and no seizures had occurred since her discharge from the hospital. Control CT scan at the same date showed a considerable decrease in the size of the cyst, along with the disappearance of its mass effect. The left lateral ventricle was unchanged.

Discussion

Serological studies have revealed that asymptomatic acquired toxoplasmosis occurs quite frequently in the general population.\(^7,8,23,36,38\) Congenital toxoplasmosis results from an acute but often subclinical maternal infection during pregnancy,\(^8,10\) However, maternal toxoplasmosis acquired during pregnancy does not necessarily result in congenital infection. A prospective study carried out on 378 pregnancies detected fetal infection in only one-third of such cases.\(^10\)

Most cases of congenital toxoplasmosis are subclinical or mild, and may be overlooked in the neonatal period, and misdiagnosed later in childhood. Moreover, many of them will not exhibit any manifesta-

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**Fig. 3.** Photomicrographs of the excised mass. **Left:** A pseudocyst body is seen with a definite capsule and filled with packed clusters of Toxoplasma organisms. H & E, × 400. **Right:** Miliary calcium deposits (arrowheads) are scattered throughout the microglial nodule. H & E, × 100.
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tions of disease during systematic follow-up examinations. Because of these clinical features, the first case of congenital toxoplasmosis affecting an infant with retinal infection was described as late as 1923, and the first demonstration of CNS involvement in a newborn infant was reported in 1939.

The brain and retina appear to be the preferred sites of toxoplasmic infection, possibly because of the low local immunity and the low issue enzyme levels. Therefore, although congenital neurotoxoplasmosis may be part of a systemic disease with multivisceral involvement, it may present as a distinct entity, as in our case.

Two major neurological patterns are consistent with congenital toxoplasmosis. There may be severe acute encephalomyelitis with meningeal inflammation, scattered necrotic lesions, and the proliferative form of the protozoan. On the other hand, the disease may exhibit chronic or delayed sequelae with psychomotor retardation, cortical atrophy, aqueductal obstruction, intracranial calcifications, and the pseudocyst form of the parasite. A third pattern, which Townsend et al. described as an "intracranial single or multiple progressive mass lesion," and Schulhof and Russell named "toxoplasmoma," is quite unusual.

By updating the comprehensive series presented in 1975 by Townsend et al., we have been able to collect 34 cases of toxoplasmic mass lesion. All the patients exhibited focal signs and/or raised intracranial pressure with papilledema. All but one case were of the acquired type. Four patients underwent surgery, only one of whom was reported in the neurosurgical literature. Only one case of congenital mass lesion has been reported. This was a newborn infant who died 6 weeks after birth. This patient exhibited signs of raised intracranial pressure. Cerebral scintigraphy was consistent with a right frontotemporal mass. The antemortem diagnosis was brain tumor, but at postmortem examination a toxoplasmic pseudotumor was found occupying the basal regions of the right cerebral hemisphere.

Our case is presented in order to stress some peculiar and somewhat puzzling features of congenital toxoplasmosis. The basic lesion in CNS involvement by Toxoplasma gondii is the microglial nodule. It is composed of peripherally located microglial cells in various stages of activity, and has a necrotic center. The free, proliferative form of the parasite is never encountered, and only rarely are pseudocysts found in or near the nodule. Other features are found to some degree, such as cell infiltrates, perivascular inflammation, granulomas, and calcium deposits. It has been suggested that only in older patients does the collection of microglial nodules reach a large size and begin to soften, giving rise to signs that mimic a cerebral tumor. The whole process often takes years, thus accounting for the acquired origin of most cases of toxoplasmic mass lesion. In fact, in cases of congenital toxoplasmosis, other severe lesions (such as cerebral malformations, hydrocephalus, and microcephalia) may be clinically apparent. These may be part of an overwhelming multivisceral infection (the so-called "septic form" of toxoplasmosis) which often leads to death in a matter of weeks.

Our case is somewhat different from the previously reported toxoplasmic expansive lesions, because the location of the nodule, rather than its size, played a major role in the mass effect. The lesion was found adjacent to the midline, lying on the anteromedial aspect of the right "cystic" ventricle. Although small in size, the mass probably occluded the ipsilateral foramen of Monro. Alternatively, the granulomatous ependymitis, which is characteristic of congenital toxoplasmosis and often gives rise to focal or diffuse periventricular and periaqueductal involvement, led to membranous thickening of the ependymal lining and obstruction of the right foramen. A partial involvement of the contralateral foramen cannot be ruled out, especially in view of the slight left ventricle enlargement found in CT scanning. Whatever the mechanism, exclusion of the right lateral ventricle had occurred, accounting for the striking growth of the right-sided "tumor" observed in our patient. The ependymal inflammation had spared the aqueduct, because no signs of third ventricle enlargement were noted on the CT scan.

The finding of scattered punctate calcium deposits (Fig. 3 right) in the subependymal nodule is consistent with the congenital origin of toxoplasmosis. These paraventricular calcifications, the occurrence of toxoplasmic pseudocysts in the absence of the proliferative form of the parasite, and the detection of low antibody titers at specific serological examinations were all signs of biologically old infection. This would suggest the inactivity of the disease, along with its possible low response to specific chemotherapeutic treatment. In the light of these findings, the growth of the tumor was ascribable to the secretary activity of the choroid plexus.

The delayed onset of the disease played a major role in misleading us as to the diagnosis, a problem that is not uncommon. In fact, it has been noted that other lesions, such as hydrocephalus and chorioretinitis (two of the main features of congenital toxoplasmosis), are rarely present in the neonatal period. These conditions are usually slow to develop, and occurrence at 6 to 10 months of age or later is not exceptional. The possible late development of the disease and its protean aspects have been described by Couvreur and Desmonts. They found that 26 out of 300 cases of congenital toxoplasmosis were diagnosed after the patient reached 14 years of age. Most late cases showed brain and/or retinal involvement; as a rule, these organs offer a greater barrier to passive diffusion of maternal antibodies than extraneural tissues.

Systematic follow-up observations are mandatory.
in order to recognize any possible delayed deterioration in those patients affected by subclinical congenital toxoplasmosis. The occurrence of multiple foci of involvement in the same patient must be also kept in mind. Discrete but scattered dissemination of toxoplasmic lesions throughout the neural axis has been demonstrated in autopsy cases. 5,8,13,28,36,38

The question is raised as to whether a late appearance of hitherto unrecognized congenital lesions may occur in our patient. We believe that this child, although apparently cured, remains at risk in regard to cerebral toxoplasmic foci which may be somehow reactivated. Long-term follow-up review will be carried out.

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F. Tognetti, E. Galassi and G. Gaist
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Address reprint requests to: Francesco Tognetti, M.D., Divisione di Neurochirurgia, Ospedale Bellaria, 40139 Bologna, Italy.