

# CENTRAL NERVOUS SYSTEM TOXOPLASMOSIS IN CHILDREN WITHOUT HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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**Abstract** - *Toxoplasma Encephalitis (TE) is rare in pediatric patients, but it is an emerging opportunistic infection in the increasing number of immunocompromised hosts. It should be considered in patients who present with fever and evolving CNS symptoms. The outcome of these patients is always poor because of delay in diagnosis. We report one case of toxoplasma encephalitis in a child without HIV infection. Clinical presentation, diagnosis and treatment, are discussed.*  
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**Key Words:** *Toxoplasmosis, encephalitis, immunocompromised host, children*

## INTRODUCTION

Acquired toxoplasmosis is a common infection after birth and has an increasing prevalence with age as detected by antibody to *T.gondii* and illustrated by its ubiquitous global distribution in most world populations (1). Only 10% of acutely infected individuals have clinical signs and symptoms. The fulminant toxoplasmosis has a predilection for the central nervous system (CNS) in patients with underlying immunosuppression such as organ and bone marrow transplant recipients, patients with cancer and AIDS (1-3). Despite its high frequency in adults with HIV infection, toxoplasma encephalitis (TE) is rare in children with AIDS. It has been reported in 29 children with HIV infection in the English literature (mostly reactivated) (1,4,5). We report one case of primary acquired cerebral toxoplasmosis in a child without HIV infection. Until today, few cases have been reported in the English language medical literature.

### Illustrative case

This 11 year-old male with right lung arterio-venous (A-V) anomaly became febrile (40 °C) and had headache and emesis in November 1996. He was admitted to hospital, and antibiotic therapy was initiated. However his fever persisted and he developed seizures, progressive changes in mental status (lethargy, confusion and coma) and right hemiparesis.

The patient has no cat or dog, and consumed only well-cooked meat. Physical examination revealed fever, hemiparesis of the right side of body with III and VI cranial nerve involvement. Fundoscopic examination was normal. In laboratory evaluation, hemoglobin was 7g/dl, hematocrit: 20% platelet count 1377000./mm<sup>3</sup> and WBC 5400 cells/mm<sup>3</sup>, (44% neutrophils, 48% lymphocytes, 8% band form), CSF analysis for antibody to herpes simplex virus (HSV1,2) and PCR (polymerase chain reaction) for HIV and herpes viruses was negative. A non-contrast CT scan of the brain showed decreased attenuation between gray and white matter with edema and mild ventricular enlargement. EEG showed diffuse slowing with no epileptiform discharges. On hospital day 5, a repeated brain CT scan with contrast showed multiple enhancing lesions specially in the left frontal and parietal lobes. On the 7th hospital day an open biopsy of left frontal lobe was performed. Necrotic brain tissue was noted with histologic evidence of CNS toxoplasmosis. Toxoplasma IgM and IgG titers were negative by IFA indirect immunofluorescent antibody test (IFA) in the serum and CSF. Treatment with sulfadiazine and pyrimethamine with folinic acid was initiated. Fever resolved after ten days of therapy and on the 35th day he was discharged with good mental status and movement. A repeated CT scan after 45 days of therapy showed persistent multifocal low density lesions with calcified rims, but no new lesions, or neurologic impairment was noted. A repeated toxoplasma serology was negative. Follow-up was continued for 12 months after treatment, he had no relapses, and laboratory evaluation for HIV serology (ELISA and Western blot) performed every 3 months up to 18 months after discharge was negative.

## DISCUSSION

In children, acquired TE is rare. In 1941, Sabin described the first cases of acute acquired toxoplasmosis in 2 children. Fatal infection occurred in one patient and self-limited encephalitis in another. In a series of adults and children Triki and (couvreur reported 5 cases of TE in children without underlying illness

(1976) (1,3,6).

Primary TE was more common in the normal child, whereas reactivation disease with TE was more frequent in the immunocompromised child (7).

EA. Khan from Texas Children's Hospital reported only 3 cases of TE in children with HIV infection and 12 cases had no reported underlying disease and were apparently immunocompetent hosts. The clinical, radiologic and serologic features were not different from those of non- HIV infected children. Of the 3 children with HIV infection and TE, two died, the outcome of 1 child was not known (7,8). None of the 12 children without AIDS fully recovered after treatment for 2 months.

The major presenting features of TE in pediatric patients are fever, mental status changes and focal neurologic signs such as hemiparesis, cranial nerve palsies, and evidence of increased intracranial pressure. Eye involvement is rare in acquired toxoplasmosis but has been reported (1,4,7). The most common organs involved in disseminated toxoplasmosis are brain, heart, lung and muscles. Typical microscopic sections of brain tissue consist of well demarcated foci of necrotizing process, with a center of necrosis, surrounded by a rim of macrophages, lymphocytes and occasionally granulocytes. Immunohistochemical staining for *T. gondii* shows variable numbers of tachyzoites and encysted bradyzoites, at the margins of necrotic foci. Demonstration of the cyst form alone does not indicate acute infection (1,6,8).

Serology of specific toxoplasma antibodies is the primary method of diagnosis. The most useful tests are the indirect fluorescent antibody test (IFA) which measures IgG or IgM antibody or both, the double sandwich IgM ELISA and IgM immunosorbent agglutination assay. The latter is the most sensitive and specific of all these assays. Other recently developed serologic assays are IgA and IgE antibody response. Negative serologic results in disseminated toxoplasmosis doesn't rule out the diagnosis, because despite active disease these patients may have no demonstrable IgM or IgG antibody. In our case, serologic testing was negative. Among the neuroradiologic procedures, CT or MRI is widely used for TE. Patients with TE have focal or multifocal abnormalities including focal areas of isodensity or hypodensity, with diffuse or ring enhancement (1,6,9). At present the most effective therapy for TE is the combination of pyrimethamine and sulfadiazine. This synergistic combination provides sequential blockade of folic acid metabolism of the replicating tachyzoite form. Folinic acid is a useful adjunct that prevents bone marrow toxicity associated with pyrimethamine. Both pyrimethamine and sulfadiazine are well - absorbed from the intestine and

across the blood brain barrier. In the immunologically normal host with, severe disease, treatment is continued for 4 to 6 weeks. In immunodeficient patients with TE the length of treatment is 6 months or longer and then continued as suppressive therapy for life (3,5,8,9). (Luft BJ, Remington JS.). Disseminated toxoplasmosis, including TE, can be a fatal disease (30-35% mortality rate), but it is treatable if recognized early (6,7).

TE is rare in pediatric patients, but it is an emerging opportunistic infection in the increasing number of immunocompromised hosts. A few cases have been reported in children without underlying illness (2,7). It should be considered in patients who present with fever and CNS symptoms. Early detection should be combined with early institution of appropriate drugs to ensure a favorable outcome (2,4,7).

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# HOW MUCH DO THE RESIDENTS OF PEDIATRICS KNOW ABOUT REHABILITATION THERAPY IN CHILDREN WITH CEREBRAL PALSY?

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*Abstract* - Rehabilitation therapy is one of the most important treatment available for children with cerebral palsy. A pediatrician is usually the first who visits these patients. To determine the residents' knowledge in this field, we designed a questionnaire to be answered by the third (last) year residents of pediatrics undergoing training in all pediatric teaching hospitals and wards in Tehran (55 trainees). All of them (100%) had good cooperation and returned the questionnaires. They evaluated themselves, knowing little (21.8%), somewhat (63.6%) and well (14.6%) about the subject. None of them had additional studies about rehabilitation therapy except that considered in their formal curricula. They also did not know much about the types of available therapies in CP children. They did not follow-up their patients during the course of rehabilitation therapy. The great majority of the residents stated that the current curriculum is not sufficient for this purpose. Our study showed that there is a strong correlation between the residents' knowledge about rehabilitation therapy and their conventional training in this field ( $P < 0.0004$ ). So we strongly suggest to consider special training in formal pediatric residency training programs in this regard.

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*Key Words:* Cerebral palsy, pediatric residents, training curriculum, rehabilitation therapy

## INTRODUCTION

Cerebral palsy is a static encephalopathy with major motor manifestations occurring almost exclusively in the first years of life (1-3). It is the most common type of motor disturbances in children, with an incidence of 1-2/1000. There is a male predominance of 1.2/1. In about 50% of cases we can not find any specific etiology for it. Other etiologic causes include:

Congenital (30%-40%), neonatal central nervous infections (5%-10%), postnatal causes like trauma, infections, severe dehydration, etc. (10-20%). Although there is no correlation between delivery problems and cerebral palsy in the majority of cases, but intrapartum events (e.g. twin pregnancies, neonatal seizures, kernicterus, etc.), especially those associated with low APGAR scores, would increase the risk of developing

CP. Cerebral palsy is not a pure and isolated disorder. It is usually accompanied by other problems such as convulsions, visual sensory and auditory disturbances, affective disorders and behavioral problems. We should pay attention to these additional problems to have a successful therapeutic plan.

Unfortunately, the diagnosis is often very late. Early signs and symptoms are very hard to detect but they can be detected by careful and systematic neurologic examination, especially by using fine rating scales designed for neonates and younger infants (i.e. Neo Neuro & Up, Infanib and Denver Developmental scales).

Differential diagnoses include: progressive encephalopathies (i.e. neurodegenerative diseases), muscle diseases, spinal problems, intracranial tumors and arteriovenous malformations, subdural effusions, hydrocephalus, movement disorders, congenital dislocation of the hips and other orthopedic disorders (1-3). We must especially rule out progressive encephalopathies (e.g. leukodystrophies) because these may worsen by rehabilitation therapies.

After correct diagnosis we should design therapeutic and educational plans. Treatment of a child with cerebral palsy is a multidisciplinary practice, needing a team of diverse specialists and sub-specialists (e.g. pediatricians, child neurologists, rehabilitation therapists, orthopedists, child neurosurgeons, child psychiatrists, clinical psychologists, social workers and others). Special political, socioeconomic, and legal support for affected children is necessary. In severely affected children the therapeutic goals are limited but do exist. The main goals are to provide maximal motor functions and preventing secondary disabilities (i.e. tertiary prevention).

It is noteworthy to state that the pediatricians are often the first who visit children with cerebral palsy. They should be familiar with their roles in approaching to these children. There are many controversies concerning the usefulness of rehabilitation therapy in affected children (3-6), but analysis of 31 related studies showed that early treatment will provide better developmental achievements (4,7,8). Although the major role of a pediatrician is early diagnosis, but this is not the end of the task. He or she should have

appropriate knowledge about the rehabilitation therapies available for these children. Pediatricians must also diagnose other accompanied disorders and treat them (9,10).

To survey pediatric the residents' knowledge about their key role in diagnosis, management and education of children with cerebral palsy, we designed the following study. The major questions to be answered by this study were:

1. How much do the final year residents of pediatrics know about rehabilitation therapy in children with cerebral palsy?

2. Is there any correlation between the residents' knowledge and factors such as their curriculum, universities and wards where they are being trained, rotations in other wards (e.g. child neurology ward), scores in upgrading examinations, etc. .

### MATERIALS AND METHODS

We designed a questionnaire consisting of 33 questions. Seven of them were background questions, gathering general information about the residents, like their teaching hospitals, universities, upgrading, examination scores, rotation in a pediatric neurology ward or rehabilitation therapy center, studies around the field of rehabilitation therapy, participation in related congresses or symposiums.

About fifteen questions were about residents' knowledge of related field (the majority of these questions were of self evaluation type).

These questionnaires were distributed among 55 residents in the final year of their training in pediatrics by one of our colleagues at their training hospitals. They were all training at hospitals affiliated to medical universities of Tehran (i.e. Tehran, Shahid Beheshti and Iran Universities of Medical Sciences). All of them responded to the questions and returned them. Then we scored the answers regarding the knowledge by likert scaling scale and then analyzed them. This study was performed in February 1998.

### RESULTS

All the fifty-five questionnaires completed by residents had been returned. The questions relating the knowledge of third year residents of pediatrics were scored and accordingly ranked as very high, high, medium, low and very low. So the residents evaluated themselves as having low (21.8%), medium (63.6%) and high (14.6%) levels of knowledge about rehabilitation therapy in children with cerebral palsy (Fig. 1).

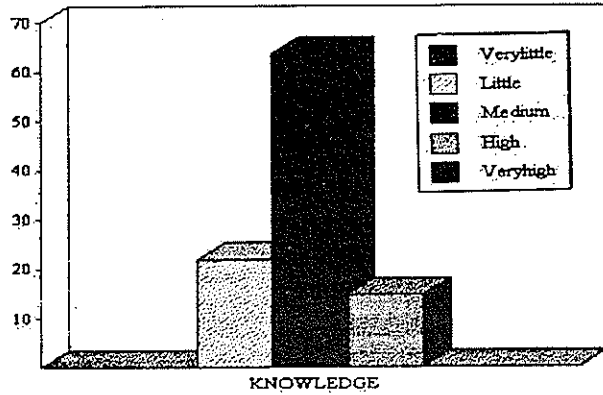


Fig. 1. Residents' knowledge about Rehabilitation therapy in CP children by self evaluating questionnaires

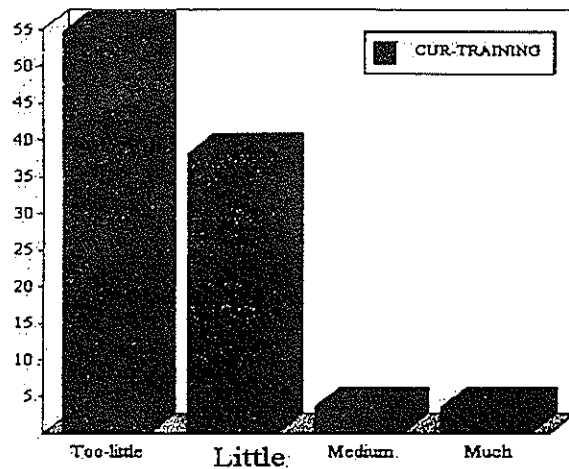


Fig. 2. Relative frequency of residents expressing their views on the efficacy of their current curriculum

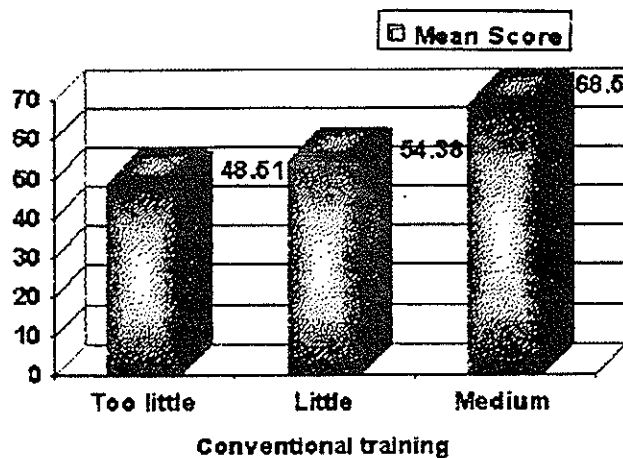


Fig. 3. Comparing mean scores of the residents' knowledge vs. their conventional training in the field

There was no significant correlation between the level of resident's knowledge and their teaching universities and hospitals, upgrading examinations' scores, rotations at other wards such as pediatric neurology ward, years of working as general physician, participation in pediatric and child neurology scientific gatherings.

It is important to state that 85.5% of the residents had never visited any rehabilitation therapy center, 10.9% had visited only once and 3.6% twice during their training course. All of the residents had no additional individual study about the field. 96.4% of the responders cited that they knew little to nothing about the current methods of physiotherapy. Regarding the methods of occupational therapy the figure was 94.6%. About the methods of speech, behavioral, family or psychotherapy the figure was 94.5%. All (100%) of the residents said that they knew little to nothing about the neurorehabilitation therapy methods. 92.8% of the responders stated that current pediatric residency curriculum was not sufficient in this field (Fig. 2).

As demonstrated in Fig. 3, there was also a strong correlation between the residents' knowledge about rehabilitation therapy and their conventional training in that field ( $P < 0.004$ ).

## DISCUSSION

Due to the important role of pediatricians in the diagnosis and management of children with cerebral palsy, residents of pediatrics should gain a good deal of knowledge in the third (last) year of residency about rehabilitation therapy in children with cerebral palsy. Unfortunately we found the reverse in this study.

This study showed that there was a strong correlation between the residents' knowledge about rehabilitation therapy and their conventional training in this field ( $P < 0.0004$ ). These results strongly suggest a curriculum revision in pediatric residency training programs. It is also better to consider actual rotations at rehabilitation therapy centers for pediatric residents,

to improve their knowledge and attitude towards the children with cerebral palsy and their management.

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