Congenital toxoplasmosis: Auditory and language outcomes in early diagnosed and treated children

Toxoplasmose congênita: evolução da função auditiva e da linguagem em crianças diagnosticadas e tratadas precocemente

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ABSTRACT

Aims: To describe the auditory and language outcomes of children with early diagnosis and treatment for congenital toxoplasmosis. **Methods:** A cross-sectional study included all children diagnosed with congenital toxoplasmosis, through the Minas Gerais State Neonatal Screening Program, from September 2006 to March 2007. All children received early treatment, initiated before the age of 2.5 months, and were periodically assisted by a team of specialists including pediatricians, ophthalmologists and speech-language therapists and audiologists. Hearing function was evaluated with the following procedures: tympanometry, transient evoked otoacoustic emissions, distortion product otoacoustic emissions, behavioral observation audiometry, and brainstem auditory evoked potentials. Hearing function and sensitivity was estimated and audiological results were classified as normal, conductive hearing loss, sensory-neural hearing loss and central dysfunction. Language performance was assessed and classified as normal or abnormal, according to test results. The following variables were studied: audiological results, neurological and ophthalmological conditions, language performance and presence of risk indicator for hearing loss other than congenital toxoplasmosis. Univariate analysis was conducted using the chi-square or Fisher's Exact test. **Results:** From September 2006 to March 2007, 106 children were diagnosed with congenital toxoplasmosis through the neonatal screening program, and were included in the study. Data analysis showed normal hearing in 60 children (56.6%), while 13 children (12.3%) had conductive hearing loss, four children (3.8%) had sensory-neural hearing loss and 29 children (27.4%) presented central hearing dysfunction. There was association between hearing problems and language deficits. The comparison between children with additional risks for hearing loss other than toxoplasmosis and children who only presented toxoplasmosis as a risk factor showed no differences. This finding suggests that audiological problems were due to congenital toxoplasmosis alone. **Conclusions:** Even with early diagnosis and treatment, a high prevalence of hearing problems and language delays was observed in children with congenital toxoplasmosis.

Keywords: TOXOPLASMOSIS, CONGENITAL/complications; TOXOPLASMOSIS, CONGENITAL/therapy; AUDITORY DISEASES, CENTRAL; AUDITORY BRAIN STEM EVOKED RESPONSES; HEARING DISORDERS; SENSORIONEURAL HEARING LOSS; HEARING IMPAIRED PERSONS; SPEECH DELAY/etiology; LANGUAGE; SPEECH, LANGUAGE AND HEARING SCIENCES.

RESUMO

Objetivos: descrever a evolução audiológica e de linguagem em crianças com toxoplasmose congênita diagnosticada e tratada precocemente. **Métodos:** um estudo transversal descritivo incluiu todas as crianças diagnosticadas com toxoplasmose congênita pelo Programa Estadual de Triagem Neonatal de Minas Gerais entre setembro de 2006 e março de 2007. Todas as crianças foram submetidas ao protocolo de tratamento com pirimetamina e sulfadiazina iniciado antes dos 2,5 meses de idade e com duração de 12 meses, tendo realizado acompanhamento pediátrico, oftalmológico e fonoaudiológico periódico. Para avaliar a audição foram usados, como instrumentos diagnósticos, medidas de imitância acústica, emissões otoacústicas evocadas por estímulo transiente e produto de distorção, potencial evocado auditivo de tronco encefálico e observação do comportamento auditivo. Foi avaliada a acuidade auditiva e as alterações auditivas foram classificadas em condutivas, neurossensoriais e retrococleares. O desempenho de linguagem foi avaliado usando-se um instrumento de avaliação do desenvolvimento da linguagem, e os resultados foram classificados como normais ou alterados. As seguintes variáveis foram estudadas:

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resultados audiológicos, condições neurológicas e oftalmológicas, linguagem e presença de fator de risco para perda auditiva além da toxoplasmose congênita. Foi realizada análise univariada pelo qui-quadrado ou teste exato de Fisher. **Resultados:** entre setembro de 2006 e março de 2007, 106 crianças foram diagnosticadas com toxoplasmose congênita pelo programa de triagem neonatal, sendo incluídas no estudo. A análise dos dados mostrou que 60 crianças apresentavam audição normal (56,6%) e 46 crianças apresentavam audição alterada, sendo 13 crianças (12,3%) com alteração condutiva, 4 (3,8%) com perda auditiva neurossensorial e 29 (27,4%) com comprometimento retrococlear. Houve associação entre presença de alteração auditiva e déficit de linguagem. A comparação entre crianças que apresentavam outro fator de risco além da toxoplasmose e crianças que apresentavam somente a toxoplasmose como fator de risco para alteração auditiva não mostrou diferenças, o que sugere que os achados audiológicos alterados encontrados neste estudo devem-se exclusivamente à toxoplasmose congênita. **Conclusões:** mesmo com o diagnóstico e tratamento precoces, observou-se elevada prevalência de comprometimento audiológico em crianças com toxoplasmose congênita.

Descritores: TOXOPLASMOSE CONGÊNITA/complicações; TOXOPLASMOSE CONGÊNITA/terapêutica; DOENÇAS AUDITIVAS CENTRAIS; POTENCIAIS EVOCADOS AUDITIVOS DO TRONCO ENCEFÁLICO; PERDA AUDITIVA NEUROSSENSORIAL; PESSOAS COM DEFICIÊNCIA AUDITIVA; ATRASO DA FALA/etiologia; LINGUAGEM; FONOAUDIOLOGIA.

INTRODUCTION

Congenital toxoplasmosis, a highly prevalent infection in the state of Minas Gerais, Brazil, with prevalence of 1:770 living births[1], is associated with auditory impairment since the 1950's. Vertically infected children may present severe neurological, visual and hearing deficits at birth, or be born asymptomatic and develop long term sequels. Early diagnosis and treatment have been associated with better prognosis, with significant reduction of both incidence and severity of sequels.[2-5] Long term follow-up studies noticed that all congenitally infected children without treatment in the first year of life developed some disability, especially visual impairment. This was true even with the absence of symptoms at birth.

A descriptive national study with congenitally infected children up to age two years found 12.5% of transient peripheral hearing deficits (caused by middle ear disease) and 33.3% of central auditory processing disorders. Hearing was normal in 54.2% of children. No sensorineural hearing losses were found. The authors concluded that congenital toxoplasmosis is an etiological factor for hearing impairment and suggested follow-up during the first years of life for these children.[6]

High prevalence of hearing problems was found in children with congenital toxoplasmosis, with and without other risk factors for hearing loss, who were serologically evaluated. Among the children without risk factors and with anti-*Toxoplasma gondii* antibodies, 5.1% had sensorineural hearing loss**,** varying from mild to profound bilateral loss.[7] Congenital toxoplasmosis is cited in another study as the second most present acute infection (12%) in children with sensorineural hearing loss. The authors claimed that sensorineural hearing loss secondary to *Toxoplasma* infection may be mild to severe, stable or progressive, and that the treatment was associated with a decrease in the prevalence of deficits.[8]

Conflicting results are described regarding audiological impairments in congenital toxoplasmosis. Some recent studies found no sensorineural hearing impairment in congenitally infected children who received early treatment,[5,9-13] though they lack accurate description of the type and the nature of the auditory results. Other studies point out that hearing problems are among parents' major concerns towards their infected children.[14]

In a two year study in the city of Belo Horizonte, capital of Minas Gerais State, from 2003 to 2004, anti-*Toxoplasma gondii* IgM was searched in 31,808 newborns through the State Neonatal Screening Program ("Programa Estadual de Triagem Neonatal de Minas Gerais" – PETN-MG) and 20 infants were identified with congenital toxoplasmosis. The prevalence was one infected newborn in 1,590 live births. All infected children received one year treatment and underwent complete hearing evaluation. Four children (21.1%) presented sensorineural hearing loss and two (10.5%) were diagnosed with conductive hearing loss. Mild and/or moderate, and also unilateral sensorineural hearing loss, were found in this study. Among the four compromised children, three had no other risk factor for hearing loss other than congenital toxoplasmosis.[15]

Following that first study, 146,307 newborns were screened in Minas Gerais from November 2006 to May 2007 (corresponding to 95% of births in that period), and 190 infants were diagnosed with congenital toxoplasmosis.[1] First hearing evaluation was conducted at the moment of diagnosis and infected children are still being followed-up. Data concerning hearing

loss and language impairments among children with congenital toxoplasmosis are scarce, especially in high prevalence regions such as the state of Minas Gerais. This fact motivated this study, which is part of a major research that aims to evaluate the impact of congenital toxoplasmosis in the state. The study aimed to describe audiological and language outcomes of children with congenital toxoplasmosis.

METHODS

The present study reports preliminary results of the neonatal screening program conducted from November 2006 to May 2007 in Minas Gerais, in which a total of 146,307 newborns were screened for toxoplasmosis (corresponding to 95% of births in that period), and 190 infants were diagnosed with congenital toxoplasmosis, resulting in a prevalence rate of 1:770 live births.[1]

This cross-sectional study includes a sample composed of all infants diagnosed with congenital toxoplasmosis by neonatal screening from November 2006 to March 2007, the first five months of the neonatal screening program. Inclusion criteria were as follows: confirmed toxoplasmic infection, beginning of treatment prior to 2.5 months of life, adherence to the drug therapy, complete hearing and language evaluation, and parents' authorization through signed consent. Children born after March 2007 were excluded, as they had not completed all necessary language and auditory evaluation procedures.

The infants had dry blood samples routinely collected in order to search for hypothyroidism, phenylketonuria, haemoglobinopathies and cystic fibrosis. The same sample was tested for anti-*Toxoplasma gondii* IgM. Children with positive or undetermined results in dry blood IgM testing, as well as their mothers, were subjected to confirmatory serum tests (anti-*Toxoplasma gondii* IgG, IgM and IgA). Congenital toxoplasmosis diagnosis was confirmed in the infant by IgM and/or IgA presence in the first two months of life, or by IgG persistence by the end of the first year of life. All confirmed cases received a 12 month treatment with pyrimethamine, sulfadiazine and folinic acid. Infant's age at the beginning of treatment should be less than 2.5 months. They also have neuroimage examinations and received regular follow-up with a pediatrician, an ophthalmologist, and a speech-language therapist and audiologist.

The following procedures were performed as part of the hearing test battery: behavioral observation audiometry, audiometric brainstem response (ABR), transient and distortion product otoacoustic emission, and tympanometry. Hearing tests were performed with children awake or in natural sleep, without the need for sedation.

The equipments used to assess auditory responses were the Biologic Navigator with software ep317 and the Otoacoustic Emissions Analyzer AuDX Plus, both from Biologic Co. (Mundelein, IL, USA) and a Middle Ear Analyzer (Interacoustics A/S, Assens, Denmark). To perform behavioral observation audiometry, the Pediatric Audiometer PA5 (Interacoustics A/S, Assens, Denmark) was used, as well as percussion instruments.

Tests results were classified as normal hearing, conductive hearing loss, sensorineural hearing loss and central dysfunction. When all tests results were within normal range, hearing was considered normal. Conductive hearing losses were considered when results showed abnormal patterns at tympanometry, evoked otoacoustic emissions were absent and ABR revealed increased absolute latencies for waves I, III and V with normal values for interpeak intervals. The criteria to classify sensorineural hearing loss was increased electrophysiological responses, increased minimum response levels in the behavioral observation audiometry, absent evoked otoacoustic emissions, and normal tympanometric curve (type A). Findings were considered as central dysfunction when abnormal patterns were observed in the ABR, for instance, asymmetric increase in absolute wave latencies for the ABR with increased interpeak intervals values or absence of replicability of response waves. Evoked otoacoustic emissions were present and cochleo-palpebral reflex was absent with type A tympanometry.

Another evaluation procedure used was a language profile protocol named Language Development Assessment (ADL). This is an assessment tool used to identify impairments in language acquisition and/or in children's development. Language domains are evaluated through receptive and expressive scales. Knowledge of language content is based in tasks focusing the concepts of quantity, quality (adjectives), spatial and temporal relations, and sequence. Language structure is assessed through morphology and syntax tasks. Results indicate if impairment is present and what is its nature (receptive, expressive or global). In this study, we analyzed deficiencies as present or absent, and the language assessment follow-up was initiated after 12 months of age (after completion of the medical treatment for congenital toxoplasmosis).

Language assessment was performed by an experienced speech-language pathologist in a quiet room and in the presence of the child's parents. Assessment procedures included free play with

age appropriate toys, pointing pictures in a story book while recognizing actions from the figures, and communication interactions. Assessment was undertaken when children had no medical problem, including conductive hearing loss. Parents routinely received orientation regarding language stimulation and information about their child's language development.

The following variables were studied: audiological results, neurological and ophthalmological conditions, language performance and presence of risk indicator for hearing loss[16] other than congenital toxoplasmosis. Ophthalmological and neurological data were taken from the children's medical records.

Data analysis was conducted through EPI INFO version 3.5. Descriptive data analysis was made and Qui-square or Fisher's exact tests were used to compare categorical variables. Confidence interval was 95% and a P value less than 0.05 was considered significant.

This study is part of a major project with the participation of the Congenital Toxoplasmosis Brazilian Group of the Universidade Federal de Minas Gerais (CTBG-UFMG) and was approved by the Ethical Research Committee from UFMG under the code ETIC 0298/06.

RESULTS

Data from 106 children identified with congenital toxoplasmosis in the first five months of the Minas Gerais State Neonatal Screening Program, whose evaluations were completed, are presented here. Results include data obtained at the last hearing and language evaluation, when children aged 18-24 months.

All children received early treatment during 12 months, starting at a mean age of 50 days (standard deviation 15.4). Of the 106 children, 58 were male (54.7%). Eleven children (10.4%) had additional risk factors for hearing loss, including very low birth weight, family history of congenital hearing loss and prolonged permanence (more than five days) in a neonatal intensive care unit.

Among the 106 children, 60 (56.6%) had normal hearing and 46 (43.4%) showed some kind of hearing impairment. The most common auditory finding was central dysfunction (n=29) which corresponded to 27.4% of the sample studied. Four children (3.8%) had sensorineural hearing loss and thirteen (12.3%) had conductive hearing loss (Figure 1).

Abnormal auditory findings did not vary when additional risk factors other than toxoplasmosis were present (Table 1). From 46 hearing impaired children studied, four (8.7%) presented additional risk factors and 42 (91.3%) had congenital toxoplasmosis as the single auditory risk factor. In the comparison between children with additional risks for hearing loss other than toxoplasmosis and children who only presented toxoplasmosis as a risk factor, the difference was not statistically significant (p=0.75).

Regarding neurological findings, 87 children (82.1%) had normal results for clinical and neuroimaging examinations and 19 (17.9%) had some kind of abnormal finding on neuroimaging. The most common finding was the presence of intracranial calcifications (n=10, 9.4%). Other neurological findings were ventricular abnormalities and microcephalus.

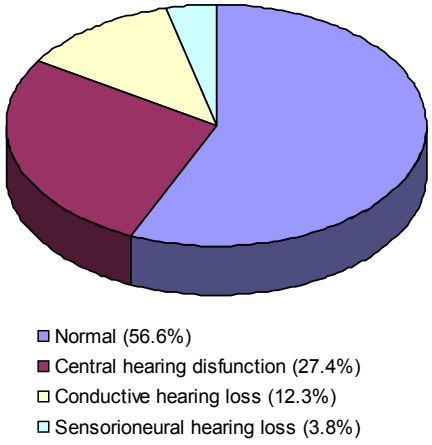

Figure 1. Percentual distribution of audiological diagnosis in 106 children with congenital toxoplasmosis identified through neonatal screening in Minas Gerais, 2008-2009.

Table 1. Univariate analysis of association between hearing impairment and presence of additional risk factors for hearing loss* in 106 children with congenital toxoplasmosis identified through neonatal screening in Minas Gerais, 2008-2009.

Hearing impairment	Presence of risk			p	OR (95% CI)
	Yes	No	Total		
Present	4	42	46	0,75	0,72 (0,19-2,62)
Absent	7	53	60		
Total	11	95	106	–	–

* Risk factors other than congenital toxoplasmosis: very low birth weight, family history of congenital hearing loss, and prolonged stay (more than 5 days) in neonatal intensive care unit.
OR: odds ratio; CI: confidence interval

Most of the sample (79.2%), which corresponds to 84 children, showed some ocular abnormality, and 22 children (20.8%) had normal ophthalmological findings. In univariate analysis, visual impairment and/or ocular lesions were not associated with hearing and/or language impairments (p=0.86 and p=0.39) (Table 2).

Table 2. Association between studied variables and language deficits in 106 children with congenital toxoplasmosis identified through neonatal screening in Minas Gerais, 2008-2009: univariate analysis.

Variables	Language Deficit		Total N=106	p	OR (95% CI)
	Present N=28	Absent N=78			
Hearing impairment					
Absent	2	58	60	0,00*	37,7(8,20-173,30)
Present	26	20	46		
Type of impairment					
Normal hearing	2	58	60	1,00	–
Sensory-neural	2	2	4	0,01*	29,00 (1,70-735,15)
Central dysfunction	19	10	29	0,00*	55,10 (9,84-408,28)
Conductive	5	8	13	0,00*	18,13 (2,45–166,94)
Ophtalmologic impairments					
Absent	22	62	84	0,86	0,94 (0,32-2,72)
Present	6	16	22		
Neurological impairments					
Absent	21	66	87	0,39	1,83 (0,63-5,25)
Present	7	12	19		
Other risks					
Absent	25	70	28	0,76	1,05(0,25-4,27)
Present	3	8	78		

* Statistical significance.
OR: odds ratio; CI: confidence interval

Language assessment revealed 28 children (26.4%) with performance under the expected normal range, according to the applied tool. Language impairments were associated with hearing impairment, and occurred only in its presence. Significant association was found in the analysis of the total sample (Table 2) and also in the comparative analysis which considered only congenital toxoplasmosis as a risk factor (withdrawing neurological abnormal findings and additional risk factors). Considering the type of auditory finding, there was an association between central dysfunction and conductive hearing losses with language impairment (Table 3).

DISCUSSION

High prevalence of hearing problems was observed in this study, even in patients with early diagnosis and treatment for congenital toxoplasmosis. Retinochoroiditis was also a very frequent finding in this same studied group, and these data point to a more virulent parasite and/or increased individual susceptibility to the infection. This hypothesis is currently under investigation in this study sample.[1] Risk of developing eye lesions in Brazilian children with congenital toxoplasmosis is five times higher than

Table 3. Association between language deficit¶ and hearing impairment¶¶ in 78 children with congenital toxoplasmosis identified through neonatal screening in Minas Gerais state (withdrawing other risk factors for hearing loss and presence of neurological impairment)

Variables	Language Deficit		Total N=78	p	OR (95% CI)
	Present N=19	Absent N=59			
Normal hearing	2	42	44	1,00	–
Sensoryneural hearing loss	1	1	2	0,12	21,00 (0,0-1420,92)
Central dysfunction	11	9	20	0,00*	25,67 (4,16-205,25)
Conductive hearing loss	5	7	12	0,00*	15,00 (1,95-143,65)

¶ Global delay on language development, vocabulary déficit.
¶¶ Sensoryneural hearing loss, conductive hearing loss and central dysfunction.
* Statistical significance.
OD: odds ratio; CI: confidence interval

in European children, and this is likely due to more virulent genotypes of the parasite in Brazil.[17]

Central auditory dysfunction, rarely mentioned in peer reviewed data, was prevalent in this study. The major negative impact of this type of hearing problem is language delay and/or impairment. Language impairments found in this study were due to central hearing dysfunction in the absence of other neurological abnormal findings. Though we should acknowledge that hearing and language development is a multifactorial process which involves all the sensory systems, environment influence as well as neuromaturation, it's our belief that one of the negative effects of toxoplasmic infection should be neuromaturational lag. The absence of differences when comparing children with additional risks for hearing loss other than toxoplasmosis and children who only presented toxoplasmosis as a risk factor, suggests that audiological problems were due to congenital toxoplasmosis alone.

Association between toxoplasmosis and three neurological disorders (epilepsy, cerebral palsy and neural deafness) was researched in Israel. The authors observed that relative risk of positive serology was significantly higher among children with neural deafness.[18]

The Chicago collaborative study found no hearing impairment. All children studied had normal ABR findings.[11,13] The Chicago collaborative cohort study assessed 30 infants and children's hearing. Children were born with congenital toxoplasmosis and had received one year treatment. ABR and behavioral observation audiometry were used as the assessment tools. No children had sensorineural hearing loss, and during the period of evaluation, results showed that six children (20%) had mild to moderate conductive hearing losses due to acute otitis media. According to the authors' statement, this prevalence didn't differ from the general population, though a number of factors may predispose this congenitally infected children to bacterial otitis media.[13] Our study found a 12.3% prevalence of conductive hearing loss, while a national study found similar results (12.5%).[6] Prevalence studies of hearing impairment in children with congenital toxoplasmosis are compared in Table 4.

A recent systematic review discusses the discrepancy between the cited prevalences in different peer reviewed data published. One argument presented sustains that studies in which the beginning of antiparasitic treatment took place before 2.5 months of life, no sensorineural hearing impairment or late onset hearing loss was observed. Therefore, differences among treatment regimens decisively influences audiological outcomes found in the different published studies. These same authors emphasize the need for repeated assessment of hearing until the age of 24-30 months.[19]

Nevertheless, the present study found a high prevalence of hearing deficits in a sample of children with congenital toxoplasmosis in whom treatment was initiated before 2,5 months of age. This result points to the possibility of increased virulence of the parasite and/or higher individual susceptibility in the studied region. It's important to notice that these are preliminary results and a more substantial contribution will certainly be possible with a larger sample and a longer follow-up.

From our point of view, hearing and language outcomes in this population of children with congenital toxoplasmosis are of major interest in the follow-up program, especially concerning the achievement of a better quality of life, preventing communication disorders and improving the academic performance of these children. Another substantial contribution would be directing the actions of a public program. To do so, it is imperative an adequate audiological and language diagnosis, as we continue to find deficits in these areas. Continued follow-up of children with congenital toxoplasmosis would therefore help to define precisely the risk of hearing and language impairments.

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Table 4. Prevalence studies of hearing impairment in children with congenital toxoplasmosis

Hearing outcome	Frequence of impairments (%)				
	McGee et al (1992)	Azevedo et al. (2000)	McLeod et al. (2006)	Andrade et al. (2008)	Present study
Normal hearing	80%	54,2%	100%	68,4%	56,6%
Sensoryoneural impairment	-	-	-	21,1%	3,8%
Conductive impairment	20%	12,5%	-	10,5%	12,3%
Central dysfunction	-	33,3%	-	-	27,4%

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