

Association Between Neuropsychiatric Morbidity and Streptococcal Infections in Children

S VISWANATHAN, PD MOSES, S VARAKKI, PS RUSSELL* AND KN BRAHMADATHAN[†]

*From the Departments of Child Health, Child and Adolescent Psychiatry, * and Microbiology[†], Christian Medical College, Vellore, Tamil Nadu, India.*

Correspondence to: Dr Prabhakar D Moses, Professor and Head, Department of Child Health Unit III, Christian Medical College, Vellore 632 004, Tamil Nadu, India.

child3@cmcvellore.ac.in

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We conducted a case control study to study the association between neuropsychiatric morbidity and group A streptococcal infections in children. Twenty two cases of neuropsychiatric morbidity were compared with 64 controls. Fourteen (63.6%) of the 22 cases were positive for ASO and/or ADNB while 21 of the 64 controls (32.8%) were positive for either or both antibodies (OR = 3.428; CI: 1.15 – 10.18; *P*=0.026). We conclude that there is a statistically significant association between neuropsychiatric morbidity and streptococcal infection in children.

Key words: *Neuropsychiatric disorders, Streptococcal infection, PANDAS.*

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Pediatric autoimmune neuropsychiatric disorder associated with Group A streptococcal infection (PANDAS) is an intriguing clinical entity. Longitudinal follow up of children with obsessive compulsive disorder (OCD) revealed that a subgroup had an episodic course characterized by acute exacerbations following group A streptococcal (GAS) infections(1-5). These observations led to the proposal of a unique subgroup of patients with neuropsychiatric disorders that could be identified by certain diagnostic criteria(6). We conducted a case-control study to assess the significance of our observation(7).

METHODS

Children aged 4-16 years attending the outpatient clinic at Christian Medical College (CMC), Vellore and found to be positive on Child Behaviour Check List (CBCL) screening for any neuropsychiatric disorder that is in the spectrum of PANDAS were selected. Children with organic brain syndromes or progressive neurologic illness and those with a history of rheumatic fever were excluded. If CBCL

was positive, diagnosis was confirmed by a child and adolescent psychiatrist based on Diagnostic and Statistical Manual-IV (DSM IV) criteria(8). Age and sex matched controls were enrolled from the out-patients clinic by screening every fifth child. For every case, three controls were enrolled.

Blood samples were collected for determining anti-streptolysin O (ASO), anti-deoxyribonuclease B (ADNB), anti-nuclear antibodies (ANA), lead, and ceruloplasmin, after obtaining informed consent from the parents. ASO and ADNB titres were measured by a nephelometric technique. ANA was estimated by an immunofluorescent technique. Cut-off values for ASO and ADNB were 300 U/mL and 500 U/mL, respectively. Lead and ceruloplasmin levels were determined by standard methods(9). ASO/ADNB titers in cases and controls were analyzed and compared by Chi square test and Odd's Ratio at 95% confidence interval.

The CBCL is a questionnaire on childhood psychopathology used extensively by clinicians to identify somatic complaints, withdrawn, anxious/

WHAT THIS STUDY ADDS?

- There is a statistically significant association between neuropsychiatric morbidity and streptococcal infections in children.

depressed symptoms, social problems, thought problems, attention problems, delinquent behaviors, aggressive behaviors, as well as sexual problems in 4-16 year individuals. It is partly validated for the Indian population. It has 113 items scored on a Likert scale(8). Diagnostic and Statistical Manual-IV edition (DSM-IV) comprises the clinical criteria available for diagnosing various child psychiatric disorders and is considered as the reference standard for making clinical diagnosis in this population(10).

RESULTS

Twenty two children (20 boys, 2 girls) with neuropsychiatric morbidity and 64 age and sex matched controls (58 boys, 6 girls) were included. Amongst the cases, 7 boys and 1 girl were 4-10 years of age, while 13 boys and 1 girl were older than 10 years of age. Amongst the controls, 21 boys and 3 girls were 4-10 years of age while 37 boys and 3 girls were older than 10 years of age.

Of the 22 cases, 6 had OCD, 6 tic disorder, 5 somatoform disorder, 2 each had trichotillomania and ADHD, while one had parasomnia. Of the 64 controls, 24 (37.5%) had respiratory illness, 13 (20.3%) had neurologic illness and 27 (42.2%) children had other unrelated conditions.

Fourteen out of 22 cases were positive for ASO/ADNB. This was significantly more than that in control group, where 21 out of 64 children were found positive (OR=3.43, CI: 1.15-10.18, $P=0.026$).

DISCUSSION

GAS infections being highly endemic in India, it is likely that the prevalence of PANDAS is relatively higher as compared to non-endemic regions; however, very little information regarding this is available in the Indian literature. Sankaranarayanan and John(11) observed that one needs to be alert to the possibility of OCD arising secondary to GAS infections in India. Hence a study was undertaken to

identify children who come under the definition of PANDAS.

Among cases, boys outnumbered girls by a ratio of 11:1. Higher prevalence of PANDAS among boys has been reported by Swedo, *et al.*(3), although the observed ratio was only 2.6:1. The mean age of the cases was 11.5 years. Interestingly, in epidemiological studies carried out in a south Indian setting, GAS infections have been found to be generally higher among boys in the 5-15 year age group(12). It is also well established that rheumatic fever tends to occur maximally in the 5-15 year age group. These data indicate that children in this age group could be best targeted for studying the prevalence of PANDAS in our population.

CBCL score was significant enough to suggest neuropsychiatric morbidity in all 22 cases and were confirmed with DSM-IV interviews. Screening them for other systemic causes of neuropsychiatric morbidity like Wilson disease, lead poisoning and collagen vascular disease did not bring out any definitive diagnosis. Determination of anti-streptococcal antibodies is a very valuable tool for the confirmation of GAS pharyngitis and its differentiation from viral pharyngitis(13). A combination of both ASO and ADNB titers will give >95% specificity and sensitivity to diagnose streptococcal infections. In the present study, laboratory evidence of GAS infection was seen in 63.6% of cases as compared to 32.8% of controls. This was statistically highly significant.

In conclusion, our study identified a group of children with neuropsychiatric morbidity with no other systemic causes and with a statistically significant evidence of recent GAS infection. Elevated ASO/ADNB response may not prove a causal association, but it may be a pointer towards its probable etiology. Follow-up of these children on a long term basis may help to prove a causal and temporal association with GAS infection and its role in the diagnostic validation of PANDAS.

Contributors: SV collected the data, recruited the controls and executed the study. PDM conceived and planned the study. SV was involved in the planning and execution of the study. PR confirmed the cases and contributed to the preparation of the manuscript. KNB performed the streptococcal antibody tests and prepared the manuscript.

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