Is Bacterial Meningitis a Risk Factor for Developing Attention Deficit Hyperactivity Disorder

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ABSTRACT

Introduction: Bacterial meningitis is a severe disease with high morbidity. Many medical conditions are known to be associated with meningitis including Attention Deficit Hyperactivity Disorder (ADHD).

The goal of the present study was to examine the frequency of ADHD in children who had had bacterial meningitis. An additional goal was to assess the odds ratio for ADHD in children who had had meningitis and children who had not had it.

Methods: The sample comprised 60 children who had had meningitis in the first year of their lives and 60 control children who had not had the disease. ADHD was assessed through the structural clinical interviews with parents according to the criteria set in DSM-IV.

Results: The total frequency of ADHD in children who had had meningitis was 62%, as compared to 5% in children who had not had the disease. The odds ratio for developing ADHD was 30.5 (95% CI = 8.5 to 109) in favor of children in the meningitis group.

Conclusion: Meningitis is a significant risk factor for developing ADHD later in childhood. Children who had meningitis need to be monitored for timely detecting and treating ADHD symptoms.

INTRODUCTION

Meningitis is identified by an abnormal number of white blood cells in cerebrospinal fluid. The incidence of bacterial meningitis is about 5 cases per 100,000 in developed countries but this may be 10 times higher in less developed countries (1). There is a different incidence rate of meningitis in relation to the socioeconomic status of the country. Some cultural reasons might, in addition, explain differences in the prevalence of meningitis. As an example of this, Gounder et al. (2) found that indigenous people in the North American Arctic have much higher rates of meningitis compared to non-indigenous populations. The exact rate of meningitis in Bosnia and Herzegovina is still unknown, as there are no studies that have examined the prevalence of the disease. The epidemiology of bacterial meningitis has been significantly reduced thanks to the widespread use of conjugate vaccines (3, 4). The incidence levels drop every year, but it is still the case that children and youngsters are most at risk of developing the disease (5). Approximately 70% of meningitis cases occur in children younger than five years. There are many medical conditions known to be connected to meningitis (6). Some of the complications following meningitis include: paralysis of cranial nerves, hemiparesis, quadriparesis, muscular hypertonus, ataxia, epilepsy, obstructive hydrocephalus, attention disorder, impaired hearing and vision, and intellectual disability (7). Neurodevelopmental functions and cognitive development can also be affected by central nervous system infections (8). The link between meningitis and attention deficit hyperactivity disorder (ADHD) is not clear enough and has not been the subject of much scientific inquiry. Existing studies have shown that ADHD is one of the most common complications of meningitis in childhood, but the strength of this relationship remains unknown (9).

Unlike meningitis, which is relatively rare in children, ADHD is one of the most frequent neurobehavioral disorders in children affecting approximately 3-7% (10, 11). The 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines ADHD as a persistent

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pattern of inattention and/or hyperactivity that is more frequent and more severe than is expected for typical children at a similar level of development (12). There are three types (presentations) of ADHD: predominantly inattentive presentation, predominantly hyperactive/ impulsive presentation and combined presentation.

The exact etiology of ADHD is still unknown, although most studies point to a biological cause of the disorder. ¹³ Cortese (14) provides an excellent review of the potential causes of ADHD ranging from anatomic to genetic correlates of the disorder. Besides a number of neuropsychological deficits present in the disorder, ADHD is also characterized by different development of the brain in comparison to controls (15). Viral and bacterial infections of the central nervous system (CNS) have been implicated as a potential causative factor in ADHD (16). When examining the relationship between some neurological conditions and ADHD, it is important to note that the majority of children with ADHD do not have a major injury of the central nervous system (CNS) and that the majority of children with a structural injury to the CNS do not present with the symptoms of ADHD (17).

There are many studies that have examined the link between ADHD and some neurological conditions. Dunn et al. (18) found that children with epilepsy have more attention problems than children without epilepsy and that 38% of children with epilepsy met the diagnostic criteria for ADHD. Bloom et al. (19) examined the prevalence of novel psychiatric diagnoses after pediatric traumatic brain injury and found that 44% of the children met the criteria for ADHD after the injury. Max et al. (20) found that 46% of children who had suffered a childhood stroke developed the symptoms of ADHD. The frequency of ADHD among children with intellectual disability was 20.4%, while the frequency among children with intellectual disability caused by organic brain injury was 25.7% (21).

There are few studies that have examined the direct relationship between meningitis and ADHD. In a study by Wait et al. (9), the authors found that all children who had had meningitis in their study (n=21) later also developed ADHD. Gau et al. (8) examined the frequency of ADHD symptoms in a sample of children who had an Enterovirus 71 infection and found that 20% of them later developed ADHD.

AIMS OF THE STUDY

Because there is a lack of studies examining the strength of the relationship between ADHD and meningitis, we

attempted to fill the gap with this study. The goals of the present study are:

- To examine the frequency of ADHD in a sample of children who had had meningitis;
- To examine the odds ratio of developing ADHD between children who had had meningitis and children without meningitis;
- To examine the moderating effect of gender on frequency of ADHD in children who had had meningitis.

METHODS

PARTICIPANTS AND PROCEDURE

This is a retrospective observational study that comprised 60 children who had been treated for meningitis in the Cantonal Hospital Zenica, Bosnia and Herzegovina, from January1,1999 to December 31, 2001. At the time of treatment for meningitis the children were aged 1 year and younger. They were treated with antibiotics and successfully cured of the disease. There were 36 boys (60%) and 24 girls (40%) in the sample. Parents of the children were interviewed about the presence of ADHD when they brought their children in for a regular medical checkup in 2007/8. At that time, the children from the meningitis group children were attending elementary school, grades 1 to 3 (mean age 7.6 years). We used a structured clinical interview according to DSM-IV criteria for establishing the diagnosis of ADHD and the cut-off criteria for diagnosing ADHD was at least six symptoms in the inattention category or six symptoms in the hyperactivity-impulsivity category. The control group consisted of children matched by age and gender to the children in the meningitis group, but who did not have any neurologic condition prior to the assessment. They were recruited through the local school in Zenica. Parents of these children were asked to come to the Cantonal Hospital Zenica and provide us with information on these children. Written consent forms from parents were received prior to the assessment. Ethical approval for this study was obtained from the Institutional Review Board at University Clinical Center Tuzla.

STATISTICAL ANALYSIS

For the data analysis, the frequency of ADHD in both groups (meningitis group and control group) was presented. The Chi-square test was used to determine if there were statistically significant differences in the frequency of ADHD in the meningitis and control groups. Furthermore, we calculated the Phi coefficient as a measure of the effect size and odds ratio to examine if and to what extent meningitis at the age of infancy increases the chances of developing ADHD later in childhood. In addition to this we checked if there were statistically significant differences in the frequency of ADHD in the meningitis group in relation to the child's gender. An alpha level of .05 was set for all statistical tests. Statistical analysis was performed with SPSS v13.

RESULTS

The first goal was to examine the overall frequency of ADHD in the meningitis group and in the control group. The results are shown in Table 1.

The results of the Chi-square test indicate a large difference in the frequency of ADHD in meningitis group and control group ($X^2(1)$ =40.8, p<.001). The Phi coefficient, as a measure of correlation between ADHD and meningitis, was moderate to large at 0.51. The odds ratio was 30.5 (95% CI = 8.5 to 109) in favor of children in the meningitis group. Children in the meningitis group had a mean of 8.3 symptoms (median 8 symptoms) according to the DSM-IV criteria and children in the control group had a mean of 7.3 symptoms (median 7 symptoms). In relation to the type of ADHD, all children (n=3) in the non-meningitis group had the predominantly hyperactive-impulsive ADHD type, while in the meningitis group 17 children had ADHD-combined type and 20 children had the predominantly hyperactive-impulsive ADHD type. None of the children had the predominantly inattentive ADHD type.

Table 1. Frequency of ADHD in meningitis group and in acontrol group of children

	AD				
With		W/o		Total	
Ν	%	Ν	%	Ν	%
37	62	23	38	60	100
3	5	57	95	60	100
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Table 2. Frequency of ADHD in children who had hadmeningitis in relation to the child's gender

	ADHD					
	With		W/o		Total	
Group	Ν	%	Ν	%	N	%
Boys	24	66.5	12	33.5	36	100
Girls	13	54.2	11	45.8	24	100

Table 2 shows the results of frequency of ADHD in relation to gender in the meningitis group.

According to the results of the Chi-square test, there were no statistically significant differences in the frequency of ADHD in relation to gender ($X^2(1) = 0.50$, p=.48). The odds ratio was 1.7 in favor of boys (95% CI= 0.6 to 4.9). The Phi coefficient, as a measure of effect size, was very small as well, 0.09.

DISCUSSION

The goal of this study was to determine the frequency of ADHD among the children who had had meningitis. The results clearly show that meningitis can be regarded as a significant risk factor for developing ADHD. The frequency of ADHD in the meningitis group was 62%, and in the control group it was 5%. Although the sample size of the control group was fairly small to determine the prevalence of ADHD in typically developing children, the frequency was found to be in accordance with existing studies. Children who had had meningitis were 30 times more likely to have ADHD than children who had not had meningitis. This finding is in agreement with existing studies (9), although not all children developed ADHD in our sample. It would be useful to know if the children who developed ADHD and children who did not develop ADHD differed in any systematical way.

Regarding the frequency of ADHD in relation to gender, the results of this study are not in line with existing studies. Most of the existing studies examining gender and ADHD have found a strong moderating effect of gender, with boys having a much higher chance of developing ADHD. The ratio reported in studies varies from 3:1-5.1, although there are studies reporting the ratio to be 9:1 in favor of boys (22). However, it might also be the case that girls are less likely to be referred for the assessment of ADHD due to their less frequent externalizing behaviors (23). This study did not find any gender effect on the frequency of ADHD. There are a couple of possible explanations for this finding. First of all, it might be the case that a gender effect does not exist. There are some studies examining ADHD in special populations, and these studies failed to find any gender effect. Buckley et al. (24) and Memisevic and Sinanovic (21)) did not find any gender effect on the ADHD in children with intellectual disability. The latter, for example, found an ADHD ratio of 1.5:1 in favor of boys in a sample of children with intellectual disability (21). Similarly, Turygin et al. (25) found an odds ratio of 1.03:1 in favor of boys in a large

sample of children at risk for developmental delay. The lack of gender effect on ADHD is also evident in children with epilepsy (18). These studies clearly show that the gender effect on ADHD is much smaller in the specific populations (children with intellectual disability, epilepsy, or who had had meningitis) than in the general population. The second and less likely explanation may be that the gender effect does, in fact, exist but was not found due to a small sample size (possibility of type 2 error).

These results can be seen as preliminary as there are no other studies examining gender effect in ADHD in children who had had meningitis. Additional studies are needed to determine the exact influence of gender on ADHD in children who had had meningitis. Another finding of this study that warrants further exploration is that not all children who had had meningitis have developed ADHD. One of the questions that the present study raised is whether the children who have ADHD due to meningitis are in some systematic way different from the children who do not have ADHD but had had meningitis. It could be the case that children with ADHD had more severe meningitis symptoms than children without it. Or it may be that a particular causative factor is responsible for subsequent ADHD. Another potential difference might lie in the differences in Intelligence Quotient between the meningitis groups with and without ADHD.

In light of the present findings it is important to create programs aimed at preventing the ADHD and reducing the symptoms in children who develop meningitis. The most common treatments for ADHD are pharmacological and behavioral. The first line of medications used in pharmacological treatment of ADHD are stimulants. They have a long-term positive effect on ADHD and are well tolerated (26). It is important to note that due to its high comorbidity with other psychiatric disorders patients with ADHD need to be followed as adults to secure best possible treatment options (27). Besides pharmacological treatments, there are many behavioral programs known to prevent and reduce ADHD symptoms in children. One such program, Fast Track, has demonstrated a statistically significant and clinically meaningful positive effect on reducing the risk of ADHD. The reduction rate was considerable at 53% (28). Similar positive effects were observed with the Summer Treatment Program for adolescents (29). These kinds of programs need to be systematically provided to children at risk of developing ADHD, such as children who had had meningitis. We believe that teachers and other school staff working with children (psychologists, speech therapists) need to be familiar with these programs and to incorporate them into their regular practice. Educational programs and behavioral training for parents have also shown a positive effect in reducing the symptoms of ADHD and they too should be part of the services offered in schools (30).

Finally, let us mention some of the limitations of this study. First of all, we did not collect some of the demographic data that might have an impact on ADHD. For example, it may be the case that the ADHD group of children had a more severe form of the meningitis than the group without it. Also, the duration of the disease as well as the exact cause of bacterial meningitis might have an impact. This was not set as a goal in this study, but these data would certainly be useful in further elucidating the link between ADHD and meningitis. Another limitation is that we did not collect information on the ADHD symptoms from the teachers, and these data would certainly increase the reliability of the present findings.

CONCLUSIONS

ADHD is a frequent disorder among children who have had meningitis. There were no differences in the frequency of ADHD between girls and boys. Knowing the risks involved, there should be specific programs aimed at preventing and reducing ADHD symptoms in children who have had meningitis.

References

- 1. Heckenberg SG, Brouwer MC, van de Beek, D. Bacterial meningitis. Handbook of clinical neurology 2013;121:1361-1375.
- 2. Gounder PP, Zulz T, Desai S, Stenz F, et al. Epidemiology of bacterial meningitis in the North American Arctic, 2000–2010. J Infection 2015;71:179-187.
- 3. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev 2010;23: 467-492.
- 4. Putz K, Hayani K, Zar FA. Meningitis Prim Care 2013;40:707-726.
- Li J, Li Y, Shao Z, Li L, et al. Prevalence of meningococcal meningitis in China from 2005 to 2010. Vaccine 2015;33:1092-1097.
- 6. Thomas DG. Outcome of paediatric bacterial meningitis 1979-1989. The Medical J Australia 1992; 157: 519-520.
- Alon U, Naveh Y, Gardos M, Friedman A. Neurological sequelae of septic meningitis. A follow-up study of 65 children. Isr Med Assoc J 1979;15:512-517.
- Gau SSF, Chang LY, Huang LM, Fan TY, et al. Attention-deficit/ hyperactivity-related symptoms among children with enterovirus 71 infection of the central nervous system. Pediatrics 2008;122:e452-e458.
- Wait JWV, Stanton L, Schoeman JF. Tuberculosis, meningitis and attention deficit hyperactivity disorder in children. J Trop Pediatr 2002;48:294-299.
- 10. DeWitt MB, Aman MG, Rojahn J. Effects of reinforcement contingencies on performance of children with mental retardation and attention problems. J Dev Phys Disabil 1997;9:101-115.

- 11. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: An updated systematic review and meta-regression analysis. Int J Epidemiol 2014;43:434-442.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders - 5th edition 2013; American Psychiatric Association.
- Faraone SV, Doyle AE. The nature and heritability of attention-deficit/ hyperactivity disorder. Child Adolesc Psychiatr Clin N Am 2001;10:299-316.
- Cortese S. The neurobiology and genetics of ADHD: What every clinician should know. Eur J Paediatr Neurol 2012;16:422-433.
- Kooij JJS. ADHD: A neurodevelopmental disorder. Eur Psychiatry 2015;30:45.
- Malhotra S, Bhatia NK, Kumar P, Hans C, Bhatia MS. The potential role of infections in Attention Deficit Hyperactivity Disorder. Delhi Psychiatry J 2011;14:361-367.
- 17. Sadock BJ, Sadock VA. Kaplan and Sadock's synopsis of psychiatry: Behavioral sciences/clinical psychiatry. Philadelphia: Lippincott Williams & Wilkins 2013.
- Dunn DW, Austin JK, Harezlak J, Ambrosius WT. ADHD and epilepsy in childhood. Dev Med Child Neurol 2003;45:50-54.
- Bloom DR, Levin HS, Ewing-Cobbs L, Saunders AE, et al. Lifetime and novel psychiatric disorders after pediatric traumatic brain injury. J Am Acad Child Adolesc Psychiatry 2001;40:572-579.
- Max JE, Mathews K, Manes FF, Robertson BA, et al. Attention deficit hyperactivity disorder and neurocognitive correlates after childhood stroke. J Int Neuropsychol Soc 2003;9:815-829.
- Memisevic H, Sinanovic O. Attention deficit hyperactivity disorder in children with intellectual disability in Bosnia and Herzegovina. Coll Antropol 2015;39:27-31.
- 22. Brown RT, La Rosa A. Recent developments in the pharmacotherapy

of attention-deficit/hyperactivity disorder (ADHD). Prof Psychol Res Pr 2002;33:591-595.

- Biederman J, Mick E, Faraone SV, Braaten E, et al. Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. Am J Psychiat 2002;159:36-42.
- Buckley S, Hillery J, Guerin S, McEvoy J, Dodd P. The prevalence of features of attention deficit hyperactivity disorder in a special school in Ireland. J Intellect Disabil Res 2008;52:156-162.
- 25. Turygin N, Matson JL, Tureck K. ADHD symptom prevalence and risk factors in a sample of toddlers with ASD or who are at risk for developmental delay. Res Dev Disabil 2013;34:4203-4209.
- 26. Fredriksen M, Halmøy A, Faraone SV, Haavik J. Long-term efficacy and safety of treatment with stimulants and atomoxetine in adult ADHD: A review of controlled and naturalistic studies. Eur Neuropsychopharmacol 2013;23:508-527.
- 27. Edvinsson D, Lindström E, Bingefors K, Lewander T, Ekselius L. Gender differences of axis I and II comorbidity in subjects diagnosed with attention-deficit hyperactivity disorder as adults. Acta Neuropsychiatr 2013;25:165-174.
- 28. Dodge KA. Conduct Problems Prevention Research Group. Fast track randomized controlled trial to prevent externalizing psychiatric disorders: Findings from grades 3 to 9. J Am Acad Child Adolesc Psychiatry 2007;46:1250-1262.
- 29. Sibley MH, Smith BH, Evans SW, Pelham WE, Gnagy EM. Treatment response to an intensive summer treatment program for adolescents with ADHD. J Atten Disord 2012;16:443-448.
- 30. Chronis AM, Chacko A, Fabiano GA, Wymbs BT, Pelham Jr.WE. Enhancements to the behavioral parent training paradigm for families of children with ADHD: Review and future directions. Clin Child Fam Psychol Rev 2004;7:1-27.