International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

The Prevalence of Streptococcal Infection and Anti-Basal Ganglia Antibodies in ADHD Pediatric Patients

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Abstract

Children who have trouble paying attention, controlling their impulses, or being hyperactive may suffer from attention-deficit/hyperactivity disorder (ADHD), a mental health condition that is largely influenced by their genes. However, other factors in their surroundings, such as exposure to certain bacteria or toxins, may also play a role in triggering or worsening their symptoms. In our study, we wanted to find out how common it is for children with ADHD to have an infection caused by a type of bacteria called group A streptococcus (GAS), and how often they have antibodies against GAS (ABGA) in their blood, which may indicate a past or ongoing infection. 60 children took part in a trial that was open, controlled, and random. They were split into two equal groups: group A had children with ADHD and group B had healthy children. We collected their demographic data such as age, sex, and ADHD risk factors. Group A had children with ADHD. Only depression was much higher in GAS+children than GAS-children (P=0.035). Other factors like attention, impulsiveness, non-planning, motor and fine motor speed were not different between GAS+ and GAS-children. Group B had healthy children. Impulsiveness and depression were much higher in GAS+children than GAS-children (P=0.001, 0.001). Other factors like attention, non-planning, motor, and fine motor speed were not different between GAS+ and GAS- children. ADHD children had more infections, GAS, and antibodies than healthy children. GAS+ADHD children had more depression than GAS-ADHD children. ADHD children had more attention, impulsiveness, and fine motor problems.

Keywords: Prevalence; Streptococcal Infection; Anti-Basal Ganglia Antibodies; ADHD; Pediatric Patients.

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Doi # https://doi.org/10.62877/38-IJCBS-24-25-19-38

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is primarily attributed to genetic factors, although environmental influences also play a role in ADHD, similar to conditions like TD (Tourette's Disorder), there is known to be a malfunction within the frontostriatal pathways, which are responsible for regulating motor functions, cognitive processes, and emotional responses [1,2]. It is hypothesized that one underlying cause of this dysfunction in the basal ganglia could be the generation of autoimmune responses - specifically, the creation of antibodies targeting the basal ganglia referred to as anti-basal ganglia antibodies [ABGA]. - which may occur due to a process called molecular mimicry following an infection by Group A Streptococcus (GAS) [3,4]. Some infections (like group A streptococcus - GAS) can cause sudden, mixed, movement (such as Sydenham's chorea) and mental disorders such as obsessive-compulsive disorders (OCD), tic disorder, ADHD in children. This has made researchers look at infective agents as possible triggers of childhood neurodevelopmental disorders, affecting basal ganglia [5-7]. A molecular mimicry mechanism might explain why the symptoms last even after GAS infection is gone [8]. Also, this type of disorders had high levels of Streptococcus (GAS) infection markers, like anti-streptolysin O (ASO) and anti-deoxyribonuclease B (anti-DNase B), and anti-basal ganglia antibodies (ABGA) [9,10]. After Kiessling and colleagues [11]. found more distractibility and hyperactivity in patients with post-streptococcal movement disorders than in healthy people, many studies have looked at the link between GAS infections, basal ganglia autoimmunity and ADHD in different ways, but with mixed results [12,13]. ADHD seems to be very important in post-streptococcal basal ganglia disorder, even more than OCD and tic disorders when they are alone: children with ADHD had more GAS infection markers than those with OCD or tic disorder; ADHD and especially hyperactivity symptoms strongly predicted anti-DNase B level; and ASO levels were related to basal ganglia size in children with ADHD [14,15]. ADHD is a common neurodevelopmental disorder that makes people have problems with attention, hyperactivity, and

impulsiveness, affecting their functioning and life outcomes [16]. ADHD starts in childhood, but it can stay in adulthood in about half of the patients as a full disorder (45–57%), or as a less severe disorder with some symptoms in 37% of them after 10 years [17].

Three studies compared GAS infection and ABGA levels of children with ADHD and no other mental disorders [12,13,18]. Only one study saw more ABGA in children with ADHD than healthy ones 30% vs. 15% [12] but two studies saw more ASO and anti-DNase B in children with ADHD [12,18]. All the studies that checked for GAS infection by taking throat swabs saw more positive results in children with ADHD than healthy ones [13,18]. Despite their differences, they all studied children, and, with the other studies, they show that patients with ADHD might be more likely to get infected by GAS, affecting their basal ganglia growth [14].

2. Patients and methods

In this open-label, parallel, randomized controlled trial, a total of 60 children took part. The participants were arranged into two matched groups: a cohort of 30 children who had been primarily diagnosed with ADHD, who were enrolled successively from our outpatient pediatric neurology clinic without any prior screening for Group A Streptococcus (GAS) infection, and a comparative group of 30 healthy children, aligned by age and gender to the ADHD group. Written consent, fully informed of the study's nature, was acquired from the parents of the patients involved.

2.1 Randomization and blindness

Participants in the study were divided into two groups through a randomized process that involved the use of computer-generated sequences and the selection from sealed, non-transparent envelopes. Group A consisted of children who had been diagnosed with ADHD, while group B (consisting of 30 individuals) was made up of healthy control children. Individuals were excluded from the study if they presented with OCD or TD. Additionally, they were excluded if they had any unrelated neurological or psychiatric conditions. Lastly, they were excluded if their full-scale intelligence quotient (IQ), according to the Wechsler Intelligence Scale for Children–Revised edition [19]. was below 85. For all participants, demographic data were collected, which included age, sex, and potential risk factors for developing ADHD. This encompassed a family history of ADHD, any unfavorable prenatal and perinatal events, or exposure to tobacco during the pregnancy period. Recurrent infections during childhood (specifically under the age of 12) were characterized as having at least three infectious episodes accompanied by fever each year for a minimum duration of one year. The types of infections considered included tonsillitis, adenoiditis, glomerulonephritis, among others [14].

2.2 Assessment of Cognitive Functions and Fine Motor Speed:

The study incorporated a detailed set of cognitive assessments for both the ADHD patients and their matched controls in order to obtain a broader range of neuropsychological data to delineate the variances between the two groups. Additionally, the objective was to identify a cognitive indicator that might correlate with signs of Group A Streptococcus (GAS) infection and the presence of anti-basal ganglia antibodies (ABGA). The cognitive functions were gauged using standard tests for various aspects: selective attention was measured by the Differences Perception Test (DPT) and the Sky Search Attention Score from the Test of Everyday Attention for Children (TEA-Ch) [20,21]. sustained attention was evaluated using DPT and Conners' Continuous Performance Test (CPT) [22]. and measures for impulse control (DPT and CPT), interference control [23]. and planning [19]. were also included. To assess fine motor speed, the study implemented the Pediatric Assessment of Neurological Soft Signs (PANESS), timing the duration it took for a participant to make 20 consecutive movements [24]. Furthermore, the results from subtests of the Wechsler Intelligence Scale for Children-Revised (WISC-R) were factored into the statistical comparison between the groups. For those undergoing methylphenidate therapy, treatment was on hold for three days prior to their assessment.

2.3 Determining Streptococcal Infection Status:

To ascertain the occurrence of streptococcal infection, throat swabs and blood specimens were gathered upon individuals' initial participation in the study. Identification of Group A Streptococcus (GAS) in throat cultures was achieved utilizing blood-agar plating and bacitracin sensitivity testing. However, since a positive culture alone could indicate carrier status rather than active infection, the confirmation of GAS colonization/infection required a positive culture, along with at least one elevated titer of either anti-streptolysin O (ASO) or anti-deoxyribonuclease B (anti-DNAseB). For the purposes of single-time-point measures in a case-control study where acute and convalescent sera were unavailable, an antibody titer was deemed elevated if it surpassed the upper limit of normal (ULN). This ULN threshold was set at a level exceeded by the top 20% of healthy control subjects [25]. The determined ULN20 values were 320 IU/mL for ASO and 400 IU/mL for anti-DNAseB. These values were established through the utilization of standard methods – Dade Behring nephelometry for ASO and hemolysin inhibition assay for anti-DNAseB. In instances where GAS was not detected in the throat, dual titer elevations were necessary as indicative of recent infection. Using a pair of antibodies in detection is noted to be exceptionally sensitive and accurate for the diagnosis of conditions following GAS infection. Additionally, to account for other variables that might affect the immune response to GAS—including age, season, a history of previous infections, or recent antibiotic treatment—relevant data were collected for all participants [25]. For the purpose of analysis, blood samples from the patients were collected in tubes containing potassium ethylenediaminetetraacetic acid (EDTA) (specifically, BD Vacutainer® spray-coated K2EDTA tubes from Becton, Dickinson and Company, based in Franklin Lakes, NJ, USA). These samples were subsequently centrifuged at approximately 24,104 x g at a temperature of 4 °C for 10 minutes, and the resulting plasma was then promptly stored at a temperature of -80 °C.

2.4 Anti-basal ganglia autoantibodies:

To measure the plasma levels of ASO (Cat. No MBS038268, MyBioSource Inc., San Diego, USA), anti-DNase B (Cat. No MBS7226468, MyBioSource Inc., San Diego, USA), and ABGA (Cat. No MBS706650, MyBioSource Inc., San Diego, USA), we used commercial, ready-made, microwell ELISA kits. We read the sample absorbance values in a 96-multiwell plate reader (Model 680 Microplate Reader, Bio-Rad, Milan, Italy) with two wavelengths: 450 nm and 655 nm (the second one as reference). We followed the ELISA protocols instructions and used the threshold values for adults given by the maker. These values showed patient positivity: ASO > 200 U/ml; anti-DNase B > 86 ng/ml; ABGA > 1.18 (as the ratio to the negative control optical density) but we also recorded the absolute titers values as continuous variables [14].

2.5 Symptoms of anxiety and depression were explored:

The Hamilton depression rating scale (HDRS) a clinician-rated scale to measure and track depression in adults. The HDRS is the most popular scale for depression. The original version has 17 items (HDRS17) about depression symptoms in the last week. The HDRS was for hospital patients and focuses on physical and sad symptoms. The scoring changes by version. For the HDRS17, the normal score is from 0 to 7 (or no depression), a moderate score is 20 or more [26]. We used the Arabic version [27]. The anxiety level was measured using the Hamilton Anxiety Rating Scale (HARS), a clinician-rated scale. The scale consisted of 40 criteria that were rated separately. Each item was scored on a 5-point scale, with each question being answered using a Likert scale. The score for each statement ranged from 0 to 4, indicating the severity of the anxiety. A total score was calculated by adding up the scores of the 14 items, resulting in a score ranging from 0 to 5 [28]. The Arabic version [27]. of the Barratt Impulsiveness Scale, version 11 (BIS-11), was used. The BIS-11, along with its older versions, was designed to measure impulsiveness. It assessed three areas of impulsiveness: motor, planning, and attention impulsiveness. The BIS-11 was a self-rating questionnaire consisting of 30 items, with scores ranging from 1 (rarely/never) to 4 (almost always/always). The total impulsiveness score was categorized as mild (60-70), moderate (70-80), or severe (80 or more). The test took approximately 10-15 minutes to complete and required a fifth-grade reading level. It was suitable for individuals aged 8 and older [29]. The Arabic version was utilized [30].

2.6 The ADHD self-report scale symptom catalog checklist:

It is a tool with 18 criteria from DSM-IV-TR. The 6 most important symptoms of ADHD are in Part A. The other 12 are in Part B. Four or more marks in Part A mean the patient has adult ADHD. Part B scoring can help to know more about the patient's symptoms. Part A has the six most telling questions [31]. The Arabic version is used here [32].

2.7 Statistical analysis

Statistical analysis was conducted using SPSS v27 (IBM©, Armonk, NY, USA). The normality of the data was verified through the Shapiro-Wilks test and histograms. Parametric data were described using mean and standard deviation (SD) and analyzed using a t-test. Non-parametric data were expressed as median and interquartile range (IQR) and analyzed using the Mann Whitney-test. Qualitative variables were presented as frequency and percentage (%) and analyzed using the Chi-square test or Fisher's exact test as appropriate. A two-tailed P-value less than 0.05 was considered statistically significant.

3. Results and Discussion

This is the scarcity of studies on anti-GAS antibodies and ABGA titers in children with ADHD. Many patients with ADHD had anti-DNase B (past GAS infections), ASO titre (recent GAS infection) and ABGA (autoimmunity). Comparing with previous studies on children with ADHD was hard due to different methods, but they also left out patients with tics, OCD, and Sydenham's chorea [14]. We found that ASO titers were twice as high as previous studies [12,13]. even with the age-related decline of the threshold [33]. The anti-DNase B rate in the adult sample was higher than a previous study on children with ADHD (81.3% vs. 60%) [13]. Both ASO and anti-DNase B were above the threshold in less patients than two prior studies [13,18]. We observed that ABGA (absorbance) was significantly higher in group A (case group) compared to control group ($P<0.05$) and ABGA were positivity insignificantly different between both groups. In the research conducted by Aguilera et al. [13]. and associates, anti-basal ganglia antibodies (ABGA) detection relied on a single measurement technique, leaving open the possibility of alternative methods yielding positive results. The occurrence of ABGA in their non-comorbid ADHD (nc-ADHD) subjects was similar to that of control groups reported in other studies, which ranged from 0% to 5%, using the same semi-quantitative ELISA [12,18]. approach. In contrast, they observed ABGA positivity in a significant proportion of individuals with sudden onset tics or OCD, at 27% [34]. aligning with findings from another research. Those showing ABGA positivity had signs of recent Group A Streptococcus (GAS) infections, including symptomatic improvement after penicillin treatment in one case, lending credibility to the employed diagnostic technique. Differing from Aguilera et al. [13]. findings, some researchers have identified ABGA along with elevated anti-streptococcal antibody levels in nc-ADHD subjects. For instance, Kiessling et al. [35]. study identified ABGA in 37% of their nc-ADHD group, with an even higher rate of 63% in ADHD patients with co-occurring conditions, using immunofluorescence as the detection method. None of the nc-ADHD group displayed concurrent increases in ASO and anti-DNAseB levels, whereas this was the case in 22% of those with comorbidities. The discrepancy in ABGA positivity rates could be due to differing measurement methodologies. In a more recent investigation by Toto et al. [12].

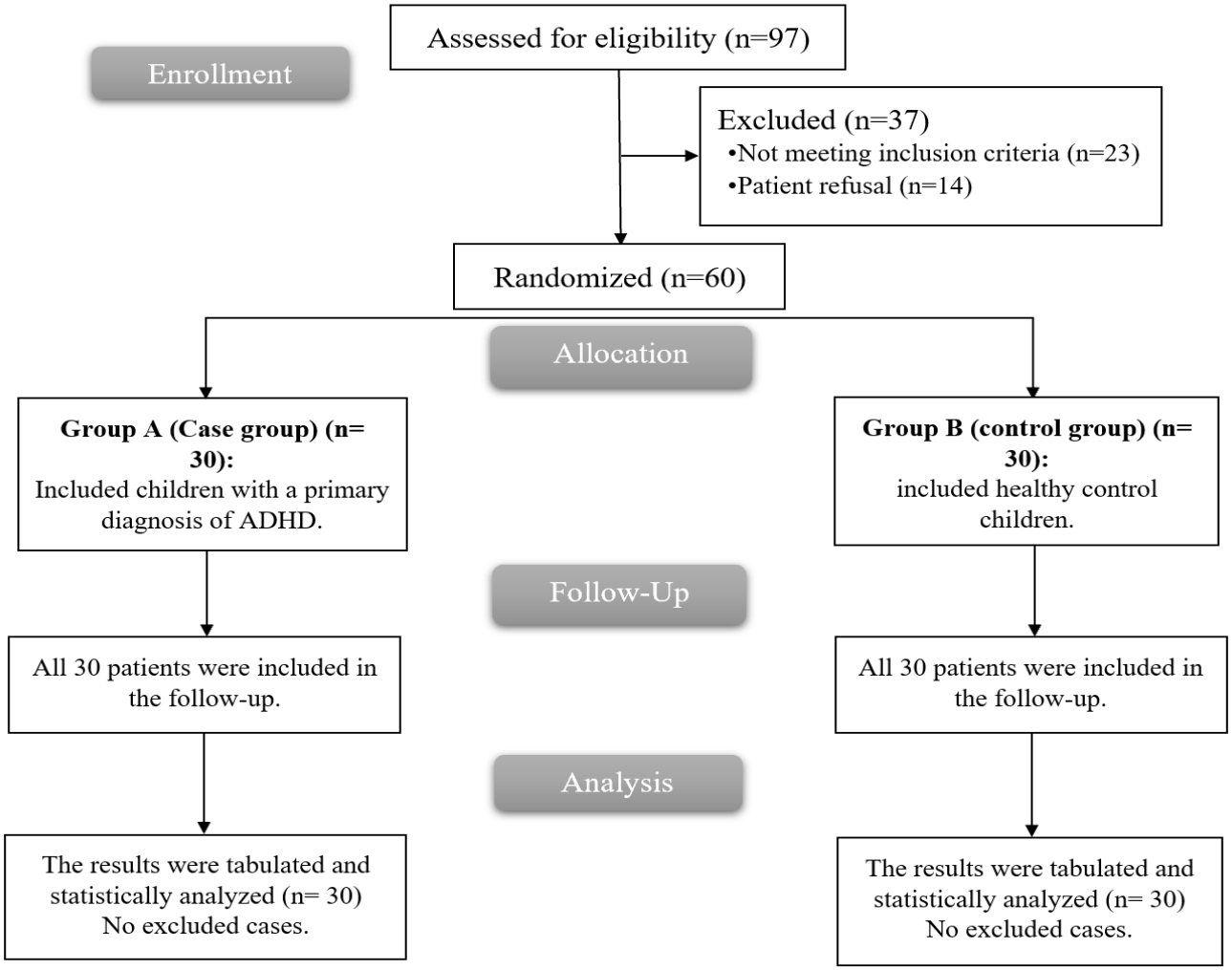

Figure 1: Consort flowchart of the enrolled patients.

Table 1: Baseline characteristics the studied groups

		Group A (Case group) (n=30)	Group B (Control group) (n=30)	P value
Age (years)		10.9 ± 3.09	10.2 ± 3.17	0.437
Sex	**Male**	27 (90%)	26 (86.67%)	0.687
	Female	3 (10%)	4 (13.33%)	
Smoking during pregnancy		12 (40%)	8 (26.67%)	0.411
Comorbidity	**Learning disorder**	12 (40%)	0 (0%)	----
	Anxiety	8 (26.67%)	0 (0%)	
	Depression	7 (23.33%)	0 (0%)	
	Oppositional-defiance disorder	2 (6.67%)	0 (0%)	
	Eating disorder	1 (3.33%)	0 (0%)	
	TD or OCD	0 (0%)	0 (0%)	

Data represented as mean ± SD or frequency (%), TD: tic disorders, OCD: obsessive compulsive disorder.

Table 2: Medical history of the studied groups

		Group A (Case group) (n=30)	Group B (Control group) (n=30)	P value
Subtypes of ADHD	**Inattentive**	8 (26.67%)	0 (0%)	----
	Combined	15 (50%)	0 (0%)	
	Hyperactive	7 (23.33%)	0 (0%)	
Familial history for ADHD		8 (26.67%)	0 (0%)	----
History of psychiatric disorders		11 (36.67%)	0 (0%)	----
Psychosocial deprivation		2 (6.67%)	0 (0%)	----

Data represented as mean ± SD or frequency (%). ADHD: attention-deficit/hyperactivity disorder.

Table 2: Clinical data of the studied groups

		Group A (Case group) (n=30)	Group B (Control group) (n=30)	P value
Any recent infection		12 (40%)	4 (13.33%)	**0.039***
Type of the recent infection	**Tonsillitis or adenoiditis with surgical removal**	5 (41.67%)	3 (75%)	0.785
	Rheumatic fever	2 (16.67%)	0 (0%)	
	Otitis	2 (16.67%)	1 (25%)	
	Mixed upper way infection	1 (8.33%)	0 (0%)	
	Glomerulonephritis	1 (8.33%)	0 (0%)	
	Pneumonia	1 (8.33%)	0 (0%)	
Recent antibiotic treatment		5 (16.67%)	2 (6.67%)	0.424
History of GAS infections		8 (26.67%)	3 (10%)	0.181
Positive swab throat culture for GAS		9 (30%)	1 (3.33%)	**0.012***
Elevated ASO		21 (70%)	8 (26.67%)	**0.002***
Elevated anti-DNAseB		21 (70%)	8 (26.67%)	**0.002***
Recent GAS infection		18 (60%)	6 (20%)	**0.004***
ASO (IU/mL)		222.8 ± 57.2	207.1 ± 55.42	0.285
Anti-DNAseB (IU/mL)		415.1 ± 101.23	310.2 ± 59.39	**<0.001***
ABGA positivity		1 (3.33%)	1 (3.33%)	NS
ABGA (absorbance)		0.08 ± 0.01	0.07 ± 0.01	**0.005***

Data represented as mean ± SD or frequency (%). GAS: group A Streptococcus, ASO: anti-streptolysin O, anti-DNAseB: anti-deoxyribonuclease B, ABGA: anti-basal ganglia antibodies, *: statistically significant as P value <0.05.

Table 4: Attention, impulsiveness, non-planning, motor, depression (HAMD) and Fine motor speed results of the studied groups.

	Group A (Case group) (n=30)				Group B (Control group) (n=30)				P value
	Total (n=30)	**GAS+ (n=18)**	**GAS- (n=12)**	**P**	**Total (n=30)**	**GAS+ (n=6)**	**GAS- (n=24)**	**P**	
Attention	21.2±6.2	19.8±6.3	22.5±5.1	0.233	17.6±6.8	20.3±5.8	16.9± 6.9	0.256	**0.045***
Impulsiveness	62.1± 18.5	63.3±19.3	60.6±13.7	0.674	40.8±12.6	56.1±15.4	37.9±9.6	**0.001***	**<0.001***
Non-planning	26.7±8.8	29.1±8.6	23.2±8.9	0.081	25.6±9.7	25.4±9.2	25.6±9.8	0.971	0.675
Motor	23.0±6.5	23.9±5.5	22.1±8.2	0.474	24.7±10.0	25.9±11.5	24.8±9.6	0.813	0.452
Depression (HAMD)	22.6±7.9	24.7±7.6	18.8±6.6	**0.035***	20.8±8.2	29.4±8	18.6±6.3	**0.001***	0.348
Fine motor speed									
Dominant hand tap (PANESS)	5.2 (3.8-6.1)	5.5 (3.9-6.2)	4.8 (3.5-5.4)	0.054	4.1 (3.1-4.9)	4.2 (3.4-5.5)	4.3 (3.1-4.9)	0.133	**0.017***
Dominant foot tap (PANESS)	6.6 (5.5-7.5)	6.6 (5.6-7.5)	6.8 (5.2-7.6)	0.195	5.8 (4.4-7)	5.8 (4.4-6.4)	6.2 (4.7-7.2)	0.725	**0.047***

Data represented as mean ± SD, median (IQR), or frequency (%). GAS: group A Streptococcus, P: p value between GAS+ and GAS-, P value: p value between total value in both groups, *: statistically significant as P value <0.05.

We included 97 patients to screening, 23 were excluded and 14 declined. The rest 60 patients were randomly split into two groups (30 each). All patients were followed and analyzed statistically (Figure 1). The baseline characteristics data, including age and sex, were insignificantly different between the two groups. Smoking during pregnancy was also similar in both groups. As for the comorbidity that only existed in group A (case group), there were 12 cases (40%) with learning disorder, 8 cases (26.67%) with anxiety, 7 cases (23.33%) with depression, 2 cases (6.67%) with oppositional-defiance disorder, and 1 case (3.33%) with eating disorder. No cases in group A had TD or OCD. (Table 1) provides further details on the comorbidity in group A. Regarding the medical history of group A (case group), the subtypes of ADHD were inattentive that was found in 8 (26.67%) cases, combined in 15 (50%) cases and hyperactive in 7 (23.33%) cases. Among the studied cases, 8 (26.67%) cases had a positive family history of ADHD, 11 (36.67%) cases had a positive history of psychiatric disorders and 2 (6.67%) cases had psychosocial deprivation (Table 2). In (Table 3) we illustrate that the presence of any recent infection, the number of positive throat swab cultures for Group A Streptococcus (GAS), the number of cases with elevated anti-streptolysin O (ASO) titers, elevated anti-deoxyribonuclease B (anti-DNAseB) titers, and the presence of recent GAS infection were all significantly higher in group A (case group) compared to the control group ($P < 0.05$). Additionally, the level of anti-DNAseB and the absorbance (ABGA) were also significantly higher in group A compared to the control group. Type of the recent infection, recent antibiotic treatment, history of GAS infections, ASO level and ABGA positivity were insignificantly different between both groups. In group A (case group), only depression (HAMD) was significantly higher in GAS+ patients compared to GAS- patients (P=0.035), whereas attention, impulsiveness, non-planning, motor and fine motor speed (dominant hand tap, dominant foot tap) were insignificantly different between GAS+ and GAS- patients. In group B (control group), only impulsiveness and depression (HAMD) were significantly higher in GAS+ patients compared to GAS- patients (P=0.001, 0.001), whereas attention, non-planning, motor, and fine motor speed (dominant hand tap, dominant foot tap) were insignificantly different between GAS+ and GAS- patients. When comparing between the main groups, the total results of attention, impulsiveness, fine motor speed (dominant hand tap, dominant foot tap) were significantly higher in group A (case group) compared to group B (control group) ($P<0.05$), other total results of non-planning, motor and depression (HAMD) were insignificantly different between both groups (Table 4). 30% of nc-ADHD participants were found to have ABGA, a much higher percentage than the 5% found in the control group, using Church et al. [36]. Within the ABGA-positive group, half also had raised ASO levels, compared to only 15% of the control group. Yet, anti-DNAseB levels were not evaluated. While the frequency of ASO elevations in ADHD patients suggested a higher occurrence of streptococcal infections, the lack of matched sample collection by season means it's unclear whether these infections and ABGA positivity are linked to ADHD or merely reflect broader GAS infection outbreaks.

Aguilera et al. [13]. and their team did not uncover more evidence of GAS infections in their ADHD cohort, even after screening for antibody elevations and checking for GAS presence in the throat. The transient nature of GAS should be noted, especially as their sampling was a one-time event. Their study faced limitations because their institution is The National Referral Center, which did not account for geographic variances in GAS outbreaks. To mitigate this issue, they compared patients and controls from the same urban area within the same season, but still did not find an increased rate of GAS infections among ADHD patients, nor was there a history to suggest that their ADHD patients had more frequent GAS infections compared to controls [36,37]. ADHD is acknowledged as a chronic ailment, with interactions between genes and environment playing a role in its pathogenesis. Heritability is estimated at 60-75%, and varied risk factors can contribute to similar outcomes [38]. Factors such as low birth weight, prematurity, and significant early social hardships have been identified in some cases, potentially interfering with the development of neural pathways implicated in ADHD [39,40]. It seems that ADHD can result from various risk pathways, as reflected in a diverse non-selective sample. The concept of complex gene-environment interactions in neurodevelopmental disorders, including Tourette syndrome (TS) or treatment-resistant OCD, sometimes garners support from evidence of autoimmunity acting as an environmental contributing factor [41]. Nonetheless, the results from Aguilera et al. [13]. group suggest that autoimmunity linked to GAS may not be relevant in nc-ADHD. Other neurodevelopmental disorders, too, have yielded inconsistent outcomes when different measurement methods are applied, contrasting with neuro-immunological insights [42]. This highlights the need for more refined models to understand the etiopathogenesis of the complex clinical manifestations of these disorders. [43]. The phenotype of ADHD, recognized by international classifications, typically differs from that described in Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS), where symptoms worsen abruptly and tend to improve swiftly post-antibiotic treatment [44]. Additionally, the categorical DSM-IV diagnosis of ADHD diverges from conditions associated with autoantibodies affecting the central nervous system, where the onset is acute or subacute, followed by a gradual recovery over weeks with treatment [45]. Efforts to uncover ABGA and evidence of GAS infections in cases of ADHD have produced mixed findings [12]. Notably, Aguilera et al. [13]. comprehensive case-control study with meticulous methodology yielded negative results. Some evidence for a temporal association between GAS infections and ADHD behaviours came from an extensive study tracking nearly 700 schoolchildren over an eight-month period, collecting data on GAS infections and ADHD behaviour monthly [13].

4. Conclusions

Our research revealed a significant association between attention deficit hyperactivity disorder (ADHD) and various indicators of recent infections, including positive throat swab cultures for Group A Streptococcus (GAS), elevated Anti-Streptolysin O (ASO) and anti-DNAseB titers, and recent GAS infections. Furthermore, children diagnosed with ADHD who tested positive for GAS displayed notably higher levels of depression, as measured by the Hamilton Depression Rating Scale (HAMD), compared to those who tested negative for GAS. Notably, children with ADHD also exhibited significantly higher scores in attention, impulsiveness, and fine motor speed measures, as demonstrated by their performance in the dominant hand and foot tapping tests. These findings underscore the connection between ADHD and the neurological parameters evaluated in our study.

List of abbreviations

Abbreviation	Sentence
ADHD	Attention-deficit/hyperactivity disorder
HDRS	Hamilton Depression Rating Scale
HARS	Hamilton Anxiety Rating Scale
GAS	Group A Streptococcus
ABGA	Anti-Basal Ganglia Antibodies
TD	Tourette's Disorder
OCD	Obsessive Compulsive Disorders
ASO	Anti Streptolysin O
Anti-DNase B	Anti Deoxyribonuclease B
IQ	Intelligence Quotient
DPT	Differences Perception Test
CPT	Continuous Performance Test
PANESS	Pediatric Assessment of Neurological Soft Signs
WISC-R	Wechsler Intelligence Scale for Children-Revised
ULN	Upper Limit of Normal
EDTA	Ethylene Diamine Tetra Acetic acid

Declarations:

- **Ethical considerations:** The study protocol was approved by the departmental committee before case collection. The protocol was discussed freely with each patient, and those accepted to participate in the study signed written fully informed consent. After completion of case collection and obtaining the study outcomes, the final approval by the Local Ethical Committee was obtained.
- **Consent for publication:** Available on reasonable request.
- **Availability of data and materials:** The associated data could be available by a reasonable request from scientists by sending email to the corresponding author.
- **Conflict of interest:** None.
- **Funding:** None.
- **Authors' contributions:** Amal Z. Ahmed.

Acknowledgment: None.

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