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Original Article

The Role of Epstein-Barr Virus in Adenoid and Tonsil Enlargement in Nigerian Children

Ikeoluwa Elizabeth Omosule[1], Onyemuchechi Ibeneche Gbujie[1], Titus Sunday Ibekwe[1], Bawa Ahmed Abimiku[2],

[1]Ear, Nose and Throat- Head and Neck Surgery Department, University of Abuja Teaching Hospital, Gwagwalada, Abuja, [2]Department of Pathology, University of Abuja Teaching Hospital, Gwagwalada, Abuja

Abstract

Background: Epstein–Barr Virus (EBV) is a lymphotropic virus that persists in lymphoid tissues such as the adenoids and tonsils and has been associated with several head and neck diseases. Because adenotonsillar enlargement is common in children, this study investigated whether EBV contributes to hypertrophy of these tissues.

Methodology: A comparative cross-sectional study was conducted at the University of Abuja Teaching Hospital involving 90 age and sex-matched children, 45 test and 45 control. Adenoid size was assessed radiologically using the Fujioka Adenoid-Nasopharyngeal Ratio (ANR), tonsil size was graded with the Brodsky system, and EBV status was determined using Chemiluminescence Immunoassay. Postoperative tissue volumes were also measured.

Results: Ninety children (test: 45; control: 45) participated; groups were age- and sex-matched (p = 0.480). Mean ages were 51.7±5.4 months (test) and 66.5±5.6 months (control). Mean Brodsky grade was 2.80±0.99, and mean ANR was 0.72±0.21.

EBV IgG prevalence for the test group was 91.1% and 8.9% were EBV negative prevalence, and 82% with 17% for control respectively. There was also a significant difference between the mean values of the EBV IgG titers in the test and control groups using the T-test analysis. T= 12.956, p= <0.001. The Odds ratio was 2.6.Only two (2) patients in the test group tested positive for EBV IgM and IgG. There was a positive correlation between EBV status and tonsil volume p=0.0320, r =0.320 and Brodsky grade r= 0.338 p= 0.023. However, the adenoid volume and ANR showed a weaker correlation with the EBV status of the test patients p= 0.466, r= 0.113

Conclusion: These findings suggest that EBV may be associated with the development and progression of **tonsillar** hypertrophy, and to a lesser extent adenoidal enlargement.

Keywords: Adenotonsillar hypertrophy, paediatric lymphoid tissue, ENT viral assessment, EBV seropositivity, adenoid hypertrophy assessment

***Correspondence:** Ikeoluwa Elizabeth Omosule, Ear, Nose and Throat Surgery Department., University of Abuja Teaching Hospital, Gwagwalada, Abuja, Email: Ike_ao@yahoo.com, Phone +2348074559547, ORCHID-0009-0002-0849-5194

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Quick Response Code:

Introduction

EBV is a ubiquitous virus that can be found in up to 85-95% of adults and children [1,2]. It is common in females between the ages of 0-25 years, and has a predilection for white ethnicity, non-smokers, and underweight people [1,2]. A study done with saliva samples using the GACRIA reagent showed that 91% of school children aged 7 years already had the antibody the EBV, which remained positive up to 11 years [2]

EBV is now considered a category 1 human tumour virus by the International Agency for Research on Cancer (IARC) in 1997[3].

EBV can be found in the tonsil tissue and adenoid of patients who had adenotonsillectomy without any clinical feature of acute illness [4,5]

To specifically diagnose acute or chronic EBV infection, serology for EBV IgM (acute phase), EBV IgG (chronic phase), or EBV DNA antibodies will usually suffice. Other serological methods will include assays for Viral Capsid antigen IgA, IgM, and IgG. Early Antigen IgA, IgM, and EBV DNA antibodies [6]. The GACRIA method can also be used for screening IgA in saliva in large populations [2]

Other methods for detecting EBV infection include In-situ Hybridization, Polymerase Chain reaction, and the Chemiluminescent immunoassay (CLIA) and ELISA [7,8]. The CLIA method is a quantitative method that can give the absolute value of viral copies present in the serum. It has a higher sensitivity compared with ELISA method. IgM 67,1% for ELISA, 92.2% FOR CLIA. Specificity of 93.8% for ELISA and 100% for CLIA [7]

Pathology of the adenotonsilar enlargement comes about in the following ways.

1. Infection from viral and bacterial agents results in inflammatory oedema, exudation, and infiltration of the adenoid and tonsil gland by inflammatory cells. This is the situation in acute infection by bacterial or viral agents. [9,10,11]

2. Chronic reactive hyperplasia is seen in the chronic presence of an infective agent or chemical agents trapped by inflammatory cells within the adenoid tissue, leading to proliferation of lymphoid cells of the gland. This results in an increase in lymphoid cells without neoplastic changes. EBV virus commonly replicates and causes trophic effect in the fossa of Rossenmuller in the nasopharynx and the Tonsilar crypts in the palatine tonsils. The consequence of this is a sustained increase in the glandular mass, causing obstruction of the nasopharyngeal airway. This is the predominant pathology in adenotonsilar hypertrophy in children[9,10].

The acute infective process alone does not give rise to sustained nasopharyngeal obstruction as the enlargement abates after treatment for infection and inflammation using antibiotics, mucosal decongestants, or antiallergic drugs. However, viruses like EBV tend to become dormant in the lymphoid tissues with recurrent periodic reactivation, which can lead to a sustained enlargement that would cause symptoms of obstruction[5]

Functional adenoid tissue is present at birth. Clinically detectable enlargement of the gland is first noticed after the child has had first contact with environmental factors[11]. This is usually when oral feeding (spoon or bottle feeding) is introduced.

This is amplified when the child starts sitting and crawling, picking dirt, and putting it in the mouth. This occurs between the ages of three to six months. Within this period, the adenoid is immunologically challenged to play its defensive role.

At about nine to eighteen months, when the child starts walking and exploring a wider environment, the child is in contact with new sets of chemicals, particles, and biological agents of infection.

The adenoid and tonsils appropriately respond by reactively going hyperplastic in the process of meeting the new immunological challenge.

However, it is known that between the ages of six to eighteen months, the adenoids spontaneously undergo hypoplastic changes(atrophy). At this time, the liver and spleen have fully matured to assume the role of immunological defense of the body. This is the situation in about 95% of the population[9]. Only about 5% will have adenoids that are active and showing reactive hyperplasia, presenting clinically with features of nasopharyngeal obstruction[11].

Adenotonsilar enlargement can occur due to infectious agents such as viruses or bacteria. It can also occur due to non-infectious agents such as exposure to tobacco smoke as second-hand smoke, gastroesophageal reflux disorders (GERD), and allergy (10). Viral agents include EBV, CMV, and Adenoviruses. Rhinoviruses, Herpes Viruses, and Coronaviruses. Bacterial agents include: Staphylococcus spp, Moraxella catarrhalis, Hemophilus Spp, Streptococcus Spp, Mycoplasma pneumonae, Neisseria Spp, and anaerobes such as Fusobacterium, Pepto streptococcus, and Prevotella Spp[9]

The commonest clinical features include snoring, mouth breathing, refusal to eat due to nasal blockage and poor weight gain in younger children, failure to thrive in extreme cases, recurrent otitis media and its sequelae, and chronic rhinosinusitis[12,13,14]

Some patients also present with dental malocclusion with anterior overbite and hypoplastic mandible, due to the lack of the stimulus of the tongue in the oral cavity, as these children are mouth breathers[9]

In severe cases, there are features of obstructive sleep apnea, bed wetting, poor school work due to daytime somnolence and hyperactivity[13,11,15]

There also seems to be a higher incidence among patients with craniofacial abnormalities[13]

Justification

Enlarged Adenoid and Tonsil tissue in children, when caused by the lymphotropic Epstein-Barr virus, is a source of significant long-term morbidity. Most times, this goes beyond chronic inflammatory changes to include a tendency for metaplastic changes later in life. The prevalence of EBV infection among children with adenotonsilar disease is not well known. This study will bridge that gap and also correlate radiographic and volumetric findings with the presence of EBV and determine if there isa need for further treatment of these patients with antivirals or preventive vaccines.

The study also provides baseline data for future studies on EBV and nasopharyngeal carcinogenesis, as the candidates may be followed up to observe the incidence of nasopharyngeal carcinoma in this group.

Aims And Objectives

Aim – To determine the correlation between EBV infection and adenotonsilar enlargement in children

Objective

To correlate the size of the adenoid and tonsils with the EBV status using radiologic and volumetric means.

Participants And Methods

The study was a comparative cross-sectional study on children 6months to -17years at theENT clinic and theatre of University of Abuja Teaching Hospital,Gwagwalada, Abuja, between July2022 and March 2023.

Ethical approval was obtained from the Ethics and Research Committee of the University of Abuja Teaching Hospital, Gwagwalada, Abuja -UATH/HREC/PR/33 (18/03/22)and West African College of Surgeons - EXM/PR/ORL/008/VOL 22 07/07/2022)

The inclusion criteria were: Paradise et al criteria for tonsillectomy. Fujioka criteria >0.67 [16], patients with Brodsky grade 2-4 [17], and sequelae. The control group was age and sex matched children without adenotonsilar symptoms, Brodsky ≤1, who presented with conditions such as cerumen auris or foreign body in the ear or nose.

The exclusion criteria included: Failure to give consent, acutely ill patients, and upper airway allergy.

The minimum sample size was determined using the Kish-Leslie formula

$n = \frac{Z^2pq}{d^2}$ to calculate sample size for population <10,000

n- sample size when population is >10,000

Z2 – confidence level 1.96 (set at 95%)

p- prevalence using the prevalence of 43% (0.43) [8]

q- 1-p =0.57

d2- set at 5%. (0.05)

Sample size = $\frac{3.84 \times 0.43 \times 0.57}{0.0025}$

n=376.5

TO CORRECT FOR POPULATION SIZE <10,000

$nf = \frac{n}{1 + \frac{n-1}{N}}$

nf— desired sample size < 10,000

n -sample size of >10,000 population

N- total population from prevalence-468

$= \frac{376.5}{1 + \frac{(376.5-1)}{46}} = 41$

To correct for attrition at 10%= 45 patients.

This would be matched in age and sex for the control population

A. Questionnaire Administration

Assents were obtained from all participants by proxy via their parents or legal caregivers since they were all minors(less than 18years) before inclusion into the study.

Demographic, socio-economic, and clinical information were obtained by proxy(via parents) for children aged below 12years, while the children aged 12 and above were guided by their parents to fill in the single researcher-administered semi-structured pretested questionnaires.

Study population - The Test group was 45 children between 6mo - 17yrs who had adenotonsillectomy and 45 otherwise healthy age and sex matched children.

B. Serology

3mls of venous blood was withdrawn(for test and control group) under aseptic conditions into sterile plain sample bottles and immediately placed in a UN3373 cold chain box at 2 to 8 degrees Celsius. This was then taken to the laboratory, and then it was spun with a Biobase high-speed centrifuge at 12000g for 5 minutes to extract the serum. 20 microliters of serum were pipetted into a Cryobase and stored at -80 degrees Celsius pending analysis.

At the time of analysis, 10µl of serum was placed into the Snibe commercial reagent kit, which uses the CLIA method with the EBV reagent to run a quantitative analysis of EBV IgG and IgM- after thawing for 1 hour.

Values were recorded in the Excel data spreadsheet corresponding to the previous data from the questionnaire.

Daily lot-to-lot validation was done for each kit.

Laboratory coats were washed and disinfected after each use and left in the laboratory. Proper hand washing was done, and hands were sanitized with 75% alcohol spray after each procedure.

C. Adenotonsillar tissue volume estimation was done (for the test group only) in 3 ways:

1- adenoid nasopharyngeal ratio- done using the Fujioka criteria at >0.67[16]

2- Brodsky grade 2 to 4 by single-person clinical estimation [17]

3- volumetric analysis- using a 50ml syringe[18]

A clean 50ml syringe was sealed at the needle end with some waterproof plaster and filled with 20mls of clean water.

All the tonsils and adenoids were dissected using the vasoconstrictive hydrolytic cold steel method[19].Suctioning was done over a piece of gauze to prevent tissue loss.

Tissues were rinsed in normal saline to remove blood and mucous and patted dry with a clean piece of gauze.

Then the adenoid tissue was dropped gently into the syringe from the plunger end, and the volume of liquid displaced was measured and recorded.

This was repeated for both tonsils using a clean 50 ml syringe with water.

Parallax error was avoided by ensuring the displacement was observed at eye level and against a white background.

The results were then recorded in the Excelsheet in the column for the corresponding patient.

Data Analysis was done using the Statistical Package for Social Sciences version 24. Quantitative variables – mean, median, standard deviation, range, and CI. Qualitative variables are in frequencies.

Correlation analysis was done using the Pearson Test. Chi-square was used to test the null and alternative hypotheses and the association between the qualitative variables. Risk assessment was done using the Odds ratio. Results were displayed in figures, texts, and tables.

Results

In the test patient category, the mean age was 51.7±5.4 months. The control group had a mean of 66.5±5.6 months(P=0.107). See Table 1

The peak age group among the test population was between 0-36months

There was a general male preponderance among all the patients who were studied, with an M:F ratio of 3.1:1 and 2.2:1 in the test and control groups, respectively. (See Table 1.1)

Snoring 40(88.9%), followed by mouth breathing 37 (82%), nasal blockage 37 (82%), and recurrent runny nose 30 (66.7%), were the commonest presenting complaints. This is similar to what is well established in the literature[12-14,20]. In terms of socioeconomic grouping, the most frequent was the patients of middle-class parents21(46.7%), followed by the upper class14 (31.1%), then 10 (22.2%) patients from lower-class families

Whereas poor weight gain 9 (20%), speech impairment 4 (8.9%), and hearing loss 1 (2.2%) had the least response. Other complaints noted were repeated sneezing 8(17.8%), ear tugging or pain 5 (11.1%). In terms of socioeconomic grouping, the most frequent was the patients of middle-class parents21(46.7%), followed by the upper class14 (31.1%), then 10 (22.2%) patients from lower-class families.

The size of the tonsils ranged from Brodsky grade 0 to 4. The mean Brodsky grade was 2.80±0.99 with a median value of 3

The Adenoid nasopharyngeal ratio ranged from 0.2 to 1, with a mean value of 0.72±0.21 and a median value of 0.8; CI: 1.16-2.09

In the volumetric analysis, the range for tonsils was 0 to 6mL, with a mean value of 2.34±1.32 and 2.05±1.25 for the right and left, respectively. The mean total tonsil volume was 4.39±2.49 with a median value of 4mls; CI -3.65-5.15

The mean adenoid volume was 1.47±1.24mls

The prevalence of EBV in the test group was 91.1% (30 M:11F), while 4 F (8.9%) were EBV negative. The mean IgG- 29.6±2.8 median of 30.0, Range = 0 - 50; CI = 23.9 -35.4. In the control group, prevalence was 82% (26 M:10 F), and 9 (17%) were IgG negative (5M:4F). The mean IgG -12.4±1.4, median of 14.2, Range of 0 - 35.5; CI=9.4 - 15.3.

There was a positive correlation between the overall tonsil volume and the EBV status ($r = 0.320$; $p = 0.032$), with the right tonsils having a bettercorrelation ($r = 0.359$; $p = 0.016$) than the left ($r = 0.258$; $p = 0.087$)

The degree of correlation of the Brodsky grade and its statistical significance with the EBV status ($r = 0.338$, $p = 0.023$) corroborates this relationship (seeTable 4)

Unlike the findings with the tonsils, this study revealed a very weak correlation that lacks statistical significance between adenoid volume ($r = 0.107$; $p = 0.486$), ANR ($r = 0.113$ $p = 0.466$), and the EBV status of the test group (although there is a difference between the mean adenoid volume and IgG status in the negative and positive test groups $p = 0.007$) (seeTable 5)

Discussion

Main findings and comparison with other studies

In the study centre, adenotonsillectomy accounts for about 48.7% of the ENT surgeries performed. An average of 114 patients is operated on annually. With an M:F ratio of 2:1,the peak age at surgery was 3 years.The peak age could be attributed to the fact that children under 5 years are more susceptible to environmental pathogens; this age also coincides well with the pathogenesis of adenotonsillar enlargement, because around this age, the adenoid enlargement begins to peak.

This finding was in keeping with Samdi [13], who found the mean age at surgery to be 3.5 ± 2.43 years, and Adedeji et al [14], but in contrast with Varkkhi [11], Tagliacani [20], and Endo et al [21], who found the peak age to be around 5.6 years

The most common histology was also reactive hyperplasia of lymphoid tissues, forming about 90%. The most consistent clinical symptoms were snoring, mouth breathing, and nasal blockage, which are consistent with what is found in African and Western literature [12-14,23].However, Chinawa et al [22] found that most patients in their series had cough, catarrh, and nasal allergies, poor weight gain, and

repeated sneezing as predominant symptoms. This could be as a result of the fact that the study was done in the paediatric clinic in acutely ill patients who had nasal allergies.

The study also showed a positive correlation between the duration of complaints and the tonsil volume(p= 0.009)as well as the IgG value (p= 0.048). This shows that children who had long-standing complaints of symptoms of tonsillar hypertrophy were more likely to have enlarged tonsils and were also more likely to have a high serological value of EBV IgG.

There was a positive correlation between the overall tonsil volume (in mls) and the EBV status (r = 0.320; p = 0.032), with the right tonsils having a better correlation (r = 0.359, p = 0.016) than the left. (r = 0.258; p = 0.087). This finding implies that a 32% increase in EBV titer will result in the same percentage increase in the overall volume of the tonsils, with the right tonsils having a stronger likelihood of being increased by about 36% while the left tonsils may not increase, but if they increase, it will be to a degree that is about 26%.The degree of correlation of the Brodsky grade and its statistical significance with the EBV status (r = 0.338, p = 0.023) corroborates the relationship between the overall tonsil volume (in mL) and the EBV status.

Similarly, when comparing the averages of the positives in the test vs control groups, there was a statistically significant difference using the T-test t= 12.956 and p value= <0.001. Odds ratio =2.6. This shows that the EBV values were higher in children with enlarged adenoids and tonsils than in the control population, and children with adenotonsillar enlargement were 2.6 times more likely to be EBV seropositive than other children. This supports the fact that the virus is associated with enlargement of the adenoids and tonsils. The higher the value of EBV IgG, the more likely it was that there was enlargement of the adenoid or tonsil.

This is in contrast with the findings of Xiaotong et al [25], who found that there was no statistically significant difference between the EBV status in adenoids and tonsils in their PCR-based tissue study

Sheishima et al [5], Gunel et al [24], and Al-Salam et al [26] found a significantly strong correlation between EBV infection and tonsillitis/ tonsillar enlargement as shown in this study.

The prevalence of EBV in the test group was 91.1% and 82% in the control group.

Sheishima et al found up to 60% of children less than 16 already had EBV infection, with a prevalence of 66% and 63% in their tonsils and adenoids, respectively. Gunel et al [24] found that EBV was the commonest virus found in patients with recurrent tonsillitis, and this was steady all year round in these patients, with prevalence as high as 53.8% for recurrent tonsillitis and 32.0% in hypertrophied tonsils

Xiaotong et al [25] found lower prevalence rates in their study group, 51.9% among patients with adenotonsillar disease. The differences in this prevalence may be due to the larger sample size, differences in climates,as well as the PCR methods used in viral studies. Studies that used serology found a higher prevalence than the PCR studies.

Clinical implications

This study shows childrenhave a higher prevalence of EBV and are likely to have surgeries at least 2 years earlier in Nigeria than in Western climes. The virus has a propensity to cause chronic inflammatory changes in lymphoid tissues. In contrast with Chinawa et al, where most of the patients were from the lower class, there was a preponderance of children from middle-class homes in this study. This finding may be due to the specific demographic of patients in the study centre. Most patients who access care in the facility use the National Health Insurance Scheme and fall within the middle and upper class, whereas most in the lower class simply cannot afford surgery and tend to default on elective surgical appointments. This underscores the need for a wider reach of Universal Health Coverage, especially for the vulnerable groups, including children.

The affected children then tend to have a longer history of complaint, probably dating from the first episode of Infectious mononucleosis till progressive enlargement of the tonsils and an eventual need for tonsillectomy.

Two (4.4%) of the participants from the test group were EBV IgM positive. This is indicative of an active infection, probably subclinical, as the patients were appropriately evaluated and found fit for surgery, which they had with satisfactory outcome. This finding is supported by Jamiyan and Seishima et al [4,5] They both had Brodsky grade 4 tonsils and adenoid nasopharyngeal ratio of 0.9. This highlights the need to maintain infectious disease control protocols at all times to reduce the risk of transmission to health care workers and other patients.

Since adenotonsillar enlargement is more of a chronic disease, it is understandable that the IgG antibody, which connotes chronic infection, would be predominant in these patients than IgM antibodies, which depict active or acute infection with the virus.

The primary infection with EBV is infectious mononucleosis, which primarily involves the tonsils. Also, the primary route of infection is the oral route, which may be why more patients with tonsil enlargement had a higher correlation than adenoid enlargement.

Limitations

This sample was limited by the sample size as it was an institution-based study. Also, a molecular confirmation with the PCR would have improved the study. The serological data and study design highlight the association between the virus and the adenoid and tonsil hypertrophy, and cannot be used for causal inference.

Recommendation.

A study to compare the EBV prevalence between tissue and serum in the same patients will be worthwhile to standardize screening protocols.

The discrepancy between the right and left tonsil could be attributed to anatomical differences in paired human organ sizes, although more research needs to be done to corroborate this in our setting.

Further research should be carried out with a larger sample size with PCR to establish a causal relationship between EBV infection, and adenotonsillar enlargement in our setting. This study also provides backing data for screening, and eventually vaccination of children against EBV infection. Also, seeing as the prevalence is just as high as it is in Western climes, there is a need for emphasis on public health education on the mode of transmission of the virus, and treatment of the primary infections, as well as re-educating health care workers on the potential risks of acquisition, and spread of the virus through unsafe theatre and clinical practices.

Conclusion

There is a statistically positive correlation between the EBV status of patients with adenotonsillar enlargement when compared with age and sex matched healthy controls. EBV antibody is prevalent in both the test and control groups of patients, but the titer values are higher in the test group

The tonsil size and Brodsky grade showed a statistically significant positive correlation with the EBV IgG quantitative status, but there was a weak correlation between the adenoid volume, adeno-nasopharyngeal ratio, and EBV IgG quantitative status.

Tables And Figures

TABLE 1: Age and sex distribution of participants

	Group				
	Test n=45	Control n=45	Total N=90		
Variables	n(%)	n(%)	n(%)	Test statistic	P-value
Age (Months)	51.7±5.4¥	66.5±5.6¥		t=1.913	0.059
Sex				χ^2=0.498	0.480
Male	34(75.6)	31(68.9)	65(72.2)		
Female	11(24.4)	14(31.1)	25(27.8)		

¥ Mean±Standard Deviation t-t test statistic χ^2-chisquare statistic

Table 1.1

Socio-economic class

Variables	Frequency(n=45)	Percent
Lower class	10	22.2
Middle class	21	46.7
Upper class	14	31.1

Table 2. Duration of complaint

*Significant at 95%

Duration of complaint for the test group

Variable	Mean±SD	Median	Confidence interval	Range
Duration(months)	24.4±3.2	18.0	17.9-30.9	1-72

Table 3: Clinical and Radiologic Volumetric Analysis

Variable	Mean SD	Median	Confidence interval	Range
Right Tonsil volume(ml)	2.34±1.32	2.00	1.95-2.74	0.00-6.00
Left Tonsil volume(ml)	2.05±1.25	2.00	1.68-2.43	0.00-6.00
Total Tonsil volume(ml)	4.39±2.49	4.00	3.65-5.15	0.00-11.00
Adenoid volume(ml)	1.63±1.55	1.00	1.16-2.09	0.00-7.00

Brodsky grade	2.80±0.99	3.00	2.50-3.09	0.00-4.00
AN ratio	0.72±0.21	0.80	0.65-0.79	0.20-1.00

Table 4: Correlating the tonsil and adenoid volume with the EBV status of Test group

EBV IGG VALUE

Variable	Mean SD	Median	Confidence interval	Range
Overall value	20.9±1.8	17.8	17.4-24.6	0-50
Test group	29.6±2.8	30.0	23.9-35.4	0-50
Control group	12.4±1.4	14.2	9.4-15.3	0-35.5

Table 5- correlating EBV IgG values with the tonsil and adenoid volume

Correlation with EBV IGG value	Correlation coefficient (r)	P-value
Right Tonsil volume(ml)	0.359	0.016*
Left Tonsil volume(ml)	0.258	0.087
Total Tonsil volume(ml)	0.320	0.032*
Adenoid volume(ml)	0.107	0.486
Brodsky grade	-0.338	0.023*
AN ratio	0.113	0.466

*Significant at 95%

Table 6: Comparing the mean IgG values in the test and control groups to know if there is a statistically significant difference using the T-test. Odds ratio-2.6

	Group			
Variable	Test Mean±SD	Control Mean±SD	t	P-value
EBV IGG value	29.6±2.8	12.4±1.4	5.428	<0.001*

*Significant at 95%

	Positive	Negative		
Variable	Mean±SD	Mean±SD	t	P-value
EBV IGG value	24.5±1.9	0.23±0.2	12.956	<0.001*

*Significant at 95%

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