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Prediction of Upper Limits of Normal Values of Anti Streptolysin 'O' Titres in Normal Healthy School Going Children of 6–16 Years

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Abstract: Antistreptolysin O test, an internationally gold standard test is widely used in detection of group A streptococcal infections and their sequelae at global level. An observational study was conducted at Bengaluru city during 2015-16. A total 454 children were randomly selected from the different schools in Bangalore city. As per the results, the sex ratio was 1:1(Male 230/454, Female 224/454) with mean age 12.58±2.63 years. The titre mean ASO value was 275.93±248.73 IU, median value was 202 IU. The average cut of ASO value was 256.53IU with good specificity (95.0%), sensitivity (88.05%), PPV (85.33%), NPV (68.93%); AUC was 0.93. The resulted findings was found to be statistically significant (P<0.01) and also this mean value will help for detection of streptococcal infections at population level (p<0.01). Majority of the cases were suffering from acute rheumatic fever (80%). Test algorithms was formulated by ROC analysis, the results showed that, the AUC of non-suppurative sequelae of Group-A streptococcal (GAS) infection of the throat (63.0%). The summing of the results concludes that, the ASO is a gold standard for the investigation of the disease progression at early stage (streptococcal and rheumatic fever). This present study will help to clinician's for diagnose streptococcal infection at greater accuracy.

Keywords: ASO, Children, ULN, streptococcal, ROC

1. Introduction

Acute rheumatic fever (ARF) is important non-suppurative sequelae of Group-A streptococcal (GAS) infection of the throat. Diagnosis of ARF, according to the Jones criteria requires evidence of antecedent GAS infection [1-2]. Positive throat cultures are obtained only in about 11% at the time of presentation of ARF. Moreover, mere presence of the organism in the throat can also indicate a carrier state which is seen in 2.5-35.41% of individuals [3]. However, the appearance of antibody to Streptolysin O (Antistreptolysin O or ASO) in serum of a patient or an increase in the ASO titre is usually indicative of recent streptococcal infection [3-4]. This is especially true when considering the diagnosis of nonsuppurativesequelae of GAS infection. Anti-streptolysin O test, an internationally standardized test is widely used in detection of group Astreptococcal infections and their sequelae [8]. Elevated or rising titres of ASO are seen in 80% or more of the cases with acute rheumatic fever. Acute and convalescent sera should be obtained and tested simultaneously to decide a rising ASO titre but this is not always feasible [10]. Hence, a single specimen when available requires to be compared with a pre-determined base line value or an upper limit of normal. Although ASO titre has provided a useful guideline to physicians this has been shown to vary with age, geographical location and site of infection. Clinical microbiology laboratories often use interpretative criteria suggested by manufacturers of commercial antibody test kits. Because such 'normal' levels may only reflect appropriate titre for adults correct interpretation of titre in children can be problematic [15]. Moreover, it is not often feasible to obtain acute and

convalescent sera. Thus, the absolute value of ASO is of diagnostic importance Hence, this study is undertaken to determine the upper limit of normal (ULN) of ASO, in normal children between the age 6-16 years [12]. The present study aims to evaluate and determine the upper limit of normal values of anti streptolysin o titres in normal healthy children of 6–16 years in and around Bengaluru city.

2. Methods

An observational study was conducted at department of Paediatric, attached to the Bangalore Medical College and Research Institute, Bengaluru for the accrual period of November 2016-May2018. Total 454 School children aged between 6-16 years normal healthy children with no history of any recent throat infection. Informed consent was obtained from the parent's. Based on the previous study by Khaled AA *et al* mean upper limit of ASLO in normal healthy children was 188+/- 52. The sample size calculation is based on, $N=z^2Є^2/d^2$ Where z=1.96, Є=52.3, d=precision=10. $N=(1.96)^2(52.3)^2/(10)^2$ = 420. The following inclusion and exclusion criteria was adopted for collecting the data sets Inclusion Criteria: the tailored data were collected from School children , demographic profile such as age, sex, class, the 2 ml of venous blood each in a Plain sample tube and EDTA tube were collected. The informed consent was obtained from study subjects and their parents(ANNEXURE 1), Privacy and confidentiality was maintained. The pre tested structured format was used for the collection of data sets. Detailed Examination of each child was done in school hours. Quantitative ASLO titers was measured with the samples and tabulated to find the exact titter of ASLO levels in our study population. Exclusion; Past history of acute rheumatic fever, Children with a recent history of throat infections, Children on any antibiotics, Acute infections and Inflammatory disorders *etc*. The collected data was analyzed by using SPSS-16.50 version. Multiple logistic regression and ROC methods was used analyzed the results.

3. Results

Table 1. *Age wise distribution and significance of ASLO titre cut off value.*

	No	ASLO titers Mean±SD	Median	Cut off value (95% UL)	Specificity (%)	Sensitivity (%)	PPV(%)	NPV(%)	P-Value
Age class									
6-10 Yrs	104(22.91%)	210.55±149.57	190	293.15	80.11	73.56	89.00	66.00	0.089
11-15Yrs	331(72.91%)	265.26±125.11	220	245.00	89.56	91.55	83.00	63.00	0.001
>15 Yrs	19(4.19%)	248.99±135.96	219	266.48	96.52	90.05	90.00	75.00	0.003
Total	454(100.0%)	241.55±130.16	236	268.55	88.73	85.03	87.33	68.00	
Gender									
Male	230(50.66%)	255.66±123.52	240	95.00	92.00	78.00	72.00	70.00	0.000
Female	224(49.33%)	248.02±129.55	225	89.00	86.00	75.00	69.00	73.00	0.032
Over crowding									
Yes	97(21.36%)	326.22±119.50	314	368.00	83.11	86.23	79.00	69.00	0.000
No	357(78.63%)	280.52±125.36	265	276.00	79.52	93.08	76.00	62.00	0.163

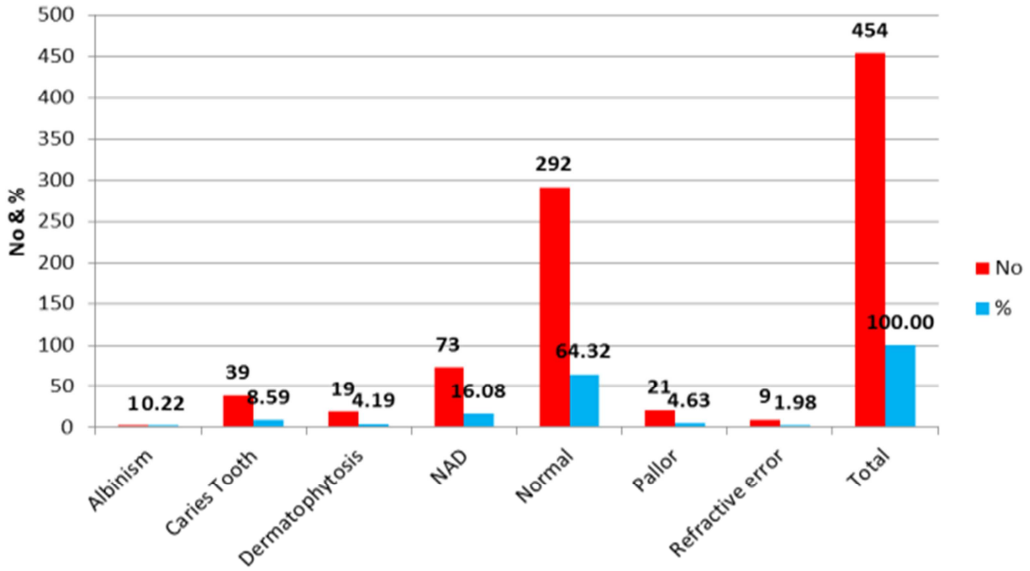

Figure 1. *Distribution of GPE in school going children's.*

A total of 454 children randomly selected from the different schools. The sex ratio 1:1(Male 230/454, Female 224/454) with mean age was 12.58±2.63 years IQR (6, 14 yrs), CI 95% (7.44-17.43 Yrs). The titre mean ASO was

275.93±248.73 IU, median 202 IU, CI 95% (-210,762.74 IU). The cut of value of ASO was 256.53 IU (obtained by receiver operating characteristic analysis) with good specificity (95.0%), sensitivity (88.05%), PPV (85.33%), NPV (68.93%), P<0.01, AUC 0.93. A more than 80% of higher than normal ASO was seen in 83 cases (18.28%), between 70-80 IU was seen in 05 (1.10%) p>0.01, 60-70 IU was seen in 09 cases p>0.01 (1.98%), 50-60 IU was observed in 18 cases (3.96%) p<0.01. The antistreptolysin O (ASO) test is the most widely used serological gold standard test (P<0.01) for the detection of Streptococcus A sequelae in exposed population, the cut off values bears in the present study was 256.53 IU and significantly correlated ULN for diagnosis of streptococous. The upper limit of normal for whole sample is 241.51 IU/ml. The frequency distribution of ASO titer of these 454 children is given below in table 1. Of these, maximum number of children is between 190 to 240 IU/ml (26%). There are also 36.5% of children who had titer between 80 to 120 IU/ml. Only 8.5% children are between 350 to 468 IU/ml. But there are about 50.0 % of children who had above> 350 IU/ml. The upper limit of normal titer for children of age group of 11 to 15 years including both lower and upper socio economic classes is 248.99 IU/ml. The GMT for all children in study group is 347 IU/ml.

4. Discussion

ASO titer level is dependent on the age group, geographical location, site of infection and socio economic class. Different studies from different areas showing different ULN of ASO in different age groups. MG Karmarkar *et al* 16 concluded that we have to constantly and periodically recheck on those very same values. Such checks may yield us results, which may serve as a foundation stone for further research on changing antigenic stimuli [10]. They also noticed that the ULN of ASO was increased from 244 IU in 1991-92 to 305 in 2001-02. Our study the titre cutoff value was found to be significantly correlated with WHO guidlines. Similar study was reported by Sunil sethi, *et al* from Chandigarh have done ASO titer on 200 healthy children of 5 to 15 years [5]. They have included children with no history of any recent throat infection in their study. ASO determination was done by stranded neutralization test. Found to have geometric mean titer (GMT) of 111.63 IU and ULN of 238.59 IU for children of 5-15 years [8]. They also observed that GMT of 113.72 IU in 5 to 10 years and 110.32 IU in 11 to 15 years age group. The ULN was found to be 230.62 IU and 242.87 IU in 5 to 10 years and 10 to 15 years respectively. Though there was a difference in ULN in both age groups it was not statistically significant G Karmarkar, et al from Mumbai have done ASO and anti D Nase B for 40 children and 160 adults in 1991-92 and also in 2001-02 of age and sex matched population. The inclusion criteria were volunteers with no features suggestive of sore throat in the past three months and no history of joint pain and not taken any antibiotic for the same. The ASO determination was done by tube dilution method [6]. Found to have ULN of ASO 244 IU during 1991 and 305 IU during 2001in children. The adults' value was 195 IU in both the years. This study showed an upward shift of ASO from 244 IU to 305 IU in 10 years in same population. No significant seasonal variation was noted in both the years. Danchin M H, *et al* from Australia have done ASO titer on 60 children in 2002. The inclusion criteria: children with no history of recent streptococcal infection. This study showed higher values in age group of 6-9 years. The ULN was 120 IU in 4-5 years, 480 IU in 6-9 years and 320 IU in 10-14 years. Zaman M M, et al from Bangladesh have estimated ASO titer on 361 apparently healthy rural school children of 5 to 14 years, and found to have GMT of 241 IU and ULN of 390 IU. The ASO titer was measured by quantitative method using an auto analyzer. Renneberg, *et al* 35 also noticed ASO in sera from children increased abruptly with increasing age in the present study the increased age was correlated 12.50 years as increases the titre value. No study yet done in literature comparing the socio economic variation even though there is a significant increase in incidence of rheumatic fever in lower socio economic group. The comparison between the lower and higher socioeconomic classes with in the age group of 5 to 10 years. The GMT is 357 IU/ml among low socioeconomic group and 242 IU/ml among high socioeconomic group. The ULN is found to be 210 IU/ml among low socioeconomic group and it is 225 IU/ml among high socioeconomic group. The difference observed is not statistically significant (p<0.01). The ASO titer seems to be influenced by various demographic factors like age, environmental factors, etc leading on to wide range of titer values, observed from different studies globally [5, 12]. It has also been reported that the upper limit of normal titer varies over a period, even within the same geographical area. All these facts necessitate to define the upper limit of normal for individual population, as well as to be confirmed periodically to observe any change in the value to higher or lower side [12].

5. Conclusion

The antistreptolysin in healthy children of age group of 5 to 15 years cut-off value is 266.68 IU/ml. This level can be taken as upper limit of normal, while considering the diagnosis of post group A Streptococcal infections in the present study population.

6. Limitation of the Study

Acute rheumatic fever is less common in children due to improved socio-economic status and health education. There are many laboratories across the city to conduct the test but without any standard baseline levels of ASLO titres. Most of the laboratories have qualitative / Semi Quantitative test to detect ASLO titres. The Study has been done, In order to have standard baseline ASLO titres for the given geographic area

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