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Mannose Binding Lectin Deficiency in pediatric patients undergoing Ear Nose and Throat surgery

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Abstract

Introduction: Tonsillectomy, adenoidectomy, adenotonsillectomy, and grommet insertion are surgical interventions performed in paediatric populations to manage obstructive symptoms, including obstructive sleep apnoea (OSA), recurrent tonsillitis, and upper respiratory tract infections (URTI). Mannose-binding lectin (MBL) deficiency, a common primary immunodeficiency, plays a role in susceptibility to infections. This study aims to examine the prevalence of MBL deficiency in children undergoing these procedures and explore its clinical significance.

Methods: A retrospective study was conducted at a paediatric ENT clinic in Perth, Western Australia, from January 2018 to December 2020. Data were collected from 1,648 paediatric patients (690 females, 957 males) aged 0-16 years undergoing adenotonsillectomy, tonsillectomy, adenoidectomy, and/or grommet insertion. Intraoperative blood samples were analysed for MBL serum levels and other immunological markers. MBL levels were classified as extremely low (<56 μg/L), low (56-1300 μg/L), or normal (>1300 μg/L). Statistical analyses were performed using R software to evaluate MBL deficiency prevalence, age at presentation, and likelihood of requiring grommet insertion.

Results: Among the study population, 33.8% exhibited MBL deficiency, with 6.0% having extremely low levels. Patients undergoing adenotonsillectomy had a higher frequency of MBL deficiency (34.7%), while those undergoing adenoidectomy alone had a prevalence of 33.7%. Contrary to the hypothesis, MBL-deficient children did not present at a younger age (ratio 1.04, 95% CI: 0.96 to 1.11, p=0.326). Female patients were 1.22 times older than male patients at presentation. Additionally, no significant association was found between low MBL levels and the necessity for grommet insertion.

Discussion: This study, with the largest sample size to date in paediatric ENT populations, underscores a high prevalence of MBL deficiency in children undergoing ENT procedures. While prior studies suggest an increased risk of infection with low MBL levels, this study found no statistically significant difference in age at presentation or need for grommet insertion. The lack of ethnic data and potential genetic variability are study limitations.

Conclusion: MBL deficiency is prevalent in paediatric patients undergoing tonsillectomy, adenoidectomy, and related procedures, affecting approximately one-third of the study cohort. Although hypothesized to present earlier or require additional interventions, MBL- deficient children did not significantly differ from non-deficient patients. Further research in larger cohorts is warranted to explore potential interventions and improve paediatric ENT outcomes.

Keywords: Mannose binding lectin; respiratory illness; adenotonsillectomy; adenoidectomy; ventilation tubes; otitis media; sleep apnoea

Introduction

Tonsillectomy, adenoidectomy, adenotonsillectomy and grommet insertion are surgical interventions performed to reduce obstructive symptoms, including obstructive sleep apnoea (OSA), reduce recurrent tonsilitis and reduce various infections spreading from the tonsils throughout the respiratory tract [1]. The palatine tonsils are lymphoepithelial tissue that comprises part of Waldeyer's ring [2] Adenoids are part of the Waldeyer's ring, sit

at the back of the nose, and help mitigate pathogens entering the nasal tract [3]. It is thought that recurrent infection may result in the development of hypertrophic tonsils and adenoids, increasing the risk of developing obstructive sleep apnoea (OSA). OSA has a severe impact on children's health and often results in poor sleep, cognitive deficits and behavioural problems impacting their development [4].

In Australia, tonsillectomy is one of the most common surgical procedures performed in the paediatric population [5] During 2012-13 in Australia, there were 724 per 100 000 children under 17 years old admitted to hospital for tonsillectomy [6]. Tonsillectomy is often performed in conjunction with adenoidectomy and grommet insertion. Upper respiratory tract infections are common in children and include tonsilitis, pharyngotonsillitis and otitis media [7]

Mannose Binding Lectin (MBL) deficiency is one of the most common immunodeficiencies in humans [8-10]. MBL is considered the most common primary human immunodeficiency in many populations [11] with one-third of the population being deficient [12]. MBL is an important calcium-dependent serum lectin protein produced in the liver that plays a role in the innate immune system in response to infection [13]. It is thought to play four key roles; complement activation, opsonophagocytosis, modulation of the inflammatory response and promotion of apoptosis [14]. It protects the host from infection through the opsonophagocytic process via the lectin pathway by binding to mannose of N-acetyl-glucosamine sugar chains present on gram- positive bacteria, gram-negative bacteria, yeast and various viruses, which activates the complement system [11,15,16]. Clinical research has shown an association between MBL deficiency and disease susceptibility [11]. Production of MBL is controlled by the MBL2 gene [15]. The MBL gene consists of four exons, with three genetic polymorphisms occurring at codons 52, 54, and 57 of exon [1,11,17,18] Polymorphisms of the structural regions of the gene or its promoter and codon variants are associated with low serum level concentrations [11,15,17-19].

MBL levels are genetically determined [12]. Contemporary research in paediatric populations suggests MBL plays an important role in their risk of acquiring an upper respiratory tract infection (URTI), including tonsilitis, otitis media (OM) and inflammation [19-21]. This is particularly important in the paediatric population aged between 6 to 24 months due to the decreased maternal derived immunoglobulins in conjunction with an immature adaptive immune system [18,21,22]. Children with recurrent OM between 2 to 4 years tend to have lower birth levels of MBL than those with few or no OM episodes [8]. Current research has not shown conclusive evidence of the relationship between MBL serum levels and adenotonsillectomy [15].

This paper reviews the prevalence of MBL deficiency in pediatric patients with significant risk factors for ENT infections, such as tonsillitis, adenoidal hypertrophy, obstructive sleep apnoea (OSA), otitis media, snoring, and glue ear. It also examines MBL deficiency in children undergoing procedures like adenotonsillectomy, adenoidectomy, grommet insertion, and turbinoplasty, which aim to reduce infection and illness in childhood.

Current Literature

Multiple studies have shown MBL polymorphisms, particularly codon 52, 54 and 57 located on exon 1, are associated with low MBL levels in children with recurrent URTI [14,15,23]. Low MBL levels make patients more vulnerable to opportunistic infections caused by gram-negative and gram-positive bacteria, as well as viruses. However, the clinical significance of MBL deficiency remains debated, particularly in the absence of other immune defects [14]. There is ongoing discussion about whether MBL serum levels, genetic mutations, or population variability play a greater role in its clinical impact. So far, most research has focused on MBL gene polymorphisms rather than serum levels [15].

Low MBL levels are an important risk factor for children undergoing tonsillectomy, adenoidectomy and adenotonsillectomy [14]. Chen demonstrated that Chinese children showed MBL serum levels were significantly lower in children with recurrent URTI than in healthy control studies [11]. Cedynski demonstrated that children with recurrent respiratory infections present with low levels of MBL twice as frequently compared to healthy controls [9]. Similarly, Koturglu suggests MBL plays a protective role in children with recurrent URTI, as such MBL deficient children may more frequently require tonsillectomy, adenoidectomy or adenotonsillectomy [14]. Vuononvirta indicated an association between MBL variants, serum levels, and nasopharyngeal bacterial colonisation, leading to recurrent infection in Finnish children [23] Healthy infants carrying MBL variants have more than twice the risk of colonization by Streptococcus pneumoniae. They are also more frequently colonized by other gram-positive bacteria, such as Staphylococcus aureus and other Staphylococcus species [23]. A significant constraint in most of the previous studies is small sample sizes. A large study with genotyping done on 1004 children showed that genotypes associated with MBL-deficiency have been shown to be at increased risk of bronchiolitis, pneumonia, wheeze with shortness of breath episodes, emergency department visits and hospital admissions for wheeze [24-26].

Methods

This study is a retrospective review of paediatric ENT patients in a centre in Perth, Western Australia. Participants were recruited from January 2018 to December 2020. There was no commercial support for this study. Data collection was conducted from January 2018 to December 2020 from patients in an ENT clinic for patients undergoing adenoidectomy, tonsillectomy, adenoidectomy and grommets. A literature search was conducted using the terms Mannose-Binding Lecture, MBL, Mannan-Binding Lectin, Tonsillectomy, Adenotonsillectomy, Respiratory Tract Infection, Upper Respiratory Tract Infection, URTI.

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The study population included participants between the ages 0 months to 16 years undergoing adenotonsillectomy, tonsillectomy, adenoidectomy with us without grommet insertion. Patients undergoing surgery had diagnoses including tonsillitis, adenoidal hypertrophy, tonsillar hypertrophy, turbinate hypertrophy, otitis media with effusion, language delay, sinusitis, recurrent tonsilitis or obstructive sleep apnoea. Ethics approval was provided by the St John of God Hospital Subiaco Human Ethics and Research Committee. Patients' blood samples were taken intraoperatively via intravenous cannula used by the anaesthetist and sent to the pathology department of 1648 patients (690 females, 957 males, age range 0-16) who attended a private otolaryngology clinic in Perth, Western Australia.

Data recorded included date of appointment, age, gender, diagnosis, surgical procedures, and blood samples. Blood samples from all patients were taken for clinical reasons to investigate recurrent ENT infection. The samples included serum ferritin, iron, transferrin saturation, MBL, IgE, IgM, IgG, IgA and haemoglobin levels. Parameters were set for each sample to establish reference values as in Table 1 below and Table 2 for MBL serum levels.

Table 1: Blood Serum Levels.

Blood Serum	High	Normal	Low
Ferritin		20-200.-0	>20.0
Iron		>10	10
Transferrin Saturation		>15%	<15%
IgE	>280		
IgM		0.4-1.6	<0.4
IgA		0.14-1.2	<0.14
Haemoglobin		105-140	<105

Table 2: MBL Serum Levels.

MBL Serum Level	
Extremely Low	<56mg/L
Low	56-1300mg/L
Normal	>1300mg/L

Ferritin ranges were considered low below 20.0, normal range between 20-200. Iron was considered low below 10.0, with normal limits between 10.0-30.-0. Transferrin Saturation was considered low below 15%, with normal ranges between 15-50%. MBL serum levels included three ranges; the highest risk of infection <56ng/mL, high risk between 56-1300 and >1300 is within normal limits. IgE was considered high above 280. IgM ranges was considered low below 0.4 with normal ranges 0.4-1.6; above 1.6 was considered high. IgG was considered low below 4.0; normal ranges 4.0-10.1; high above 10.1. IgA was considered low below 0.14; normal ranges were between 0.14-1.2. Haemoglobin was considered low below 105; normal range between 105-140.

Statistical Analysis

Results were analysed using R Core Team 2020 software via the R Studio IDE. The primary research question was the prevalence of MBL deficiency in children who undergo adenoidectomy, tonsillectomy, adenotonsillectomy and/or grommet insertion. This was analysed using epiR t-test with 95% confidence interval. The MBL levels were further divided between extremely low and low as per Table 2: MBL serum levels with extreme low <56mg/L, low 56-1300mg/L and normal ranges >1300mg/LFurther sub-analysis considered the age of presentation, with the hypothesis that MBL deficient children present at a younger age. Age presentation was analysed using linear regression of the natural logarithm of the patient age and MBL deficiency, adjusting for gender.

Results

The data collected totalled 1648 patients. A total of 1461 patients underwent adenoidectomy with 492 (33.7%) MBL deficient and 969 (66.3) patients presented with normal MBL serum levels. Patients undergoing adenotonsillectomy totalled 882, with 306 (34.7%) presenting MBL deficient and 576 (65.3%) presenting normal MBL serum levels. Patients undergoing other ENT operations in conjunction with adenotonsillectomy included 765 patients with 250 (32.6%) MBL deficient and 515 (67.3%) with normal MBL serum levels.

Given the immunity gap of children between 6-24 months where maternally derived immunoglobulins decrease due to moving from breastfeeding to solids with a still immature immune adaptive system, we hypothesised that MBL deficient children would present at a younger age with clinical symptoms in comparison with to non-deficient MBL children. Statistical analysis of the age of presentation demonstrated that MBL deficient patients are the same age as patients with normal MBL levels (ratio 1.04, 95% CI: 0.96 to 1.11, p-value: 0.326). On average, the mean age of females was 1.22 times older than male patients. We also sought to understand whether children undergoing adenoidectomy, tonsillectomy or adenotonsillectomy were more likely to undergo grommet insertion in conjunction with the surgical procedure if they were MBL deficient. The odds ratio for grommet insertion in children with extremely low MBL levels (<56 µg/L) did not indicate a higher likelihood of requiring the procedure in this group. This was also the case in children with low MBL levels (56-1300mg/L). These results are shown below in Table 3.

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Summary of characteristics of data.

Variable	Results
Gender	
Female	690 (41.9)
Male	957 (58.1)
Missing	1 (0.1)
Age at appointment	Mean 4.0
	Standard Deviation 2.9
MBL Category	
Normal Homozygote	1034 (62.7)
Heterozygote (>56 <1300)	457 (27.7)
Homozygote Abnormal <56	99 (6.0)
Missing data	58 (3.5)

Table 3: Odds ratio of grommet insertion for patients undergoing adenoidectomy, tonsillectomy or Adenotonsillectomy with MBL deficiency.

Term	Estimate Low Confidence	High Confidence	P-Value
MBL <56mg/L	0.71 0.03	17.98	0.8078
MBL >1300mg/L	0.87 0.70	1.09	0.2287

Discussion

In a large cohort, we demonstrated the prevalence of children in the study population undergoing adenotonsillectomy or other operations present with 34.7% frequency of MBL deficiency (extremely low or low). For the population with adenoidectomy only, the frequency of MBL deficient patients was 33.7%. This indicates a higher prevalence of MBL deficiencies associated with patients undergoing adenoidectomy, tonsillectomy, or adenotonsillectomy than the generation population. This supports current literature indicating low serum MBL levels increase the risk of children developing URTI impacting their otolaryngological health. Susceptibility to infection during childhood impacts their development as a result of missed schooling and learning opportunities [4].

We hypothesised children with MBL deficiency present at a younger age and were more likely to present with otitis media requiring grommet insertion. Statistical analysis demonstrated, on average, the age of MBL deficient patients was not younger than patients with normal MBL levels indicating that MBL deficient patients do not present at a younger age. Female patients were 1.22 times older than male patients upon initial presentation. We also did not find that MBL deficient patients were more likely to require grommet insertion in conjunction with adenoidectomy or adenotonsillectomy.

Our research adds to the literature of the importance of MBL deficiency with the largest sample size in the paediatric ENT population. It outlines that a significant portion of children (33.8%) presenting for otorhinolaryngological health concerns are MBL deficient. This demonstrates the need for further research surrounding the relationship between ENT health conditions such as tonsilitis, OSA, URTI and the impact of MBL on the development of ill health in the paediatric population. Despite decades of research, currently, there is no cure or treatment for MBL deficiency. Further research in a larger sample size for patients undergoing grommet insertion after or in conjunction with adenotonsillectomy may create a statistically significant result.

Limitations

There are several limitations to this study. Research suggests different ethnicities influence the levels of MBL deficiency in populations. Due to the nature of a retrospective study, there was a lack of data available on the ethnicity of patients presenting during the data collection. In a minority of patients in the data collection, not all information was available. On occasion, there was an interruption in the delivery of the serum to the pathology and in cases insufficient serum was available to be analysed to the pathology. Although our cohort study is the largest sample size to date (n=1648), larger cohort studies could allow for further relationships between MBL and infection to be examined, particularly with respect to the age of presentation as no statistical significance was found.

Conclusion

This retrospective study examines the prevalence of MBL deficiency in children who undergo adenoidectomy, tonsillectomy or adenotonsillectomy and grommets. We found that 33.8 percent of children undergoing a surgical procedure were MBL deficient. We hypothesised that MBL deficient children presented at a younger age and also were more likely to present with otitis media requiring grommet insertion, but neither hypothesis was supported by our study.

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