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Title of master thesis

LITERATURE REVIEW: PECULIARITIES OF CHILDREN WITH INFECTIOUS MONONUCLEOSIS

Submitted in partial fulfillment of the requirements for the degree of Master of Medicine

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SUMMARY

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Research title: Peculiarities of children with infectious mononucleosis.

Aim: To outline typical and atypical cases of infectious mononucleosis caused by Epstein-Barr virus in children.

Objectives:

1. To evaluate the epidemiology of infectious mononucleosis in Lithuania.

2. To review literature regarding clinical features, laboratory findings, modes of diagnostics and methods of treatment of infectious mononucleosis.

3. To discuss complications within various cases of infectious mononucleosis.

Methodology: Research databases such as Pubmed, UptoDate, and Blood Journal were utilized. A range of search terms was used to make the primary search including “Infectious Mononucleosis”, “EBV”, and “Kissing disease”. These were then put into an advanced search engine to include other relevant terms such as “Children”, and “Peculiarities”. An initial review of the presented articles was performed on the basis of ‘year of publication’, ‘the abstract’s content’ and ‘title’. After extensive reviewing, a number of articles were deemed appropriate. The final step was to assess the relevance of the topic to the specific objective by thoroughly analyzing.

Results: From the 23 selected articles: 18 were used to evaluate complications, 3 were used to evaluate atypical cases of IM and 2 were used to represent different diagnostic methods and future in vaccine development.

From the 1507 reported cases of IM in Lithuania over the previous 5 years, the highest incidence was among the 0-9 years old age group (73.5%) and the rest were in the 10-17 years age group (26.5%) (CI 95%, P<0.05). According to gender, 54.94% of those were male (828), while the remaining 45.06% were female (679). (ratio of 1.22:1) (male: female).

Conclusion:

1. The incidence of IM in Lithuania is higher among boys then girls (54.94% of boys) and among the younger children (less than 9 yrs. old).

2. Literature revealed that most common clinical features in IM are sore throat, lymphadenopathy and fatigue. Treatment for IM in most cases is conservative. Diagnosis can be usually confirmed with a combination of serological tests. Further research into vaccine development may serve as the future in decreasing complications associated with EBV.
3. Literature showed that complications could be further categorized according to their disease course (acute, long-term) and rarity. Certain complications revealed a possible pathophysiological development leading from EBV (e.g. splenic rupture, encephalitis, pharyngitis, respiratory obstruction, Burkitt lymphoma) while others are not yet fully understood (Alice in Wonderland syndrome, multiple sclerosis, acute kidney injury). Atypical cases of EBV and hemolytic uremic syndrome and Henoch-Schonlein purpura have been reported.
ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to Dr. Eglė Tamulevičienė for her patience, guidance and encouragement throughout my final year project. Her efforts and excellent teaching enabled me to develop an understanding and interest of the subject.

CONFLICT OF INTEREST

I, Hytham Dafalla the author report no conflicts of interest.

BIOETHICS CLEARANCE

No real patient data were involved in this study.

TERMS

There were no relative terms used in this study.
ABBREVIATIONS

IM – Infectious mononucleosis

EBV – Epstein Barr virus

HUS – Hemolytic uremic syndrome

HSP – Henoch-Schönlein purpura

URTI – Upper respiratory tract infection

TTP - Thrombotic thrombocytopenic purpura

GP350- Glycoprotein 350

CMV- Cytomegalovirus

LPD- Lymphoproliferative disease

SLE – Systemic lupus erythematos

AIWS- Alice in Wonderland syndrome

ULAC- Užkrečiamujų ligų ir AIDS centras

AIDS- Autoimmune deficiency syndrome

HIV – Human immunodeficiency virus

HLH - Haemophagocytic lymphohistiocytosis

MS – Multiple sclerosis
INTRODUCTION

Infectious mononucleosis (IM), has multiple synonyms such as "mono" or the "kissing disease", it is primarily caused by the virus known as Epstein-Barr virus (EBV) but can also be caused by multiple other pathogens. Approximately 90% of cases are associated with EBV; the remaining 10% can be contributed to Human herpes virus 6, Cytomegalovirus and Herpes simplex virus 1. [5] The majority of the world is already infected with the EBV virus as between 90-95% of the global population shows serologic evidence. This virus is also easily spreadable, by simple oral contact due to the way it resides in bodily secretions, especially in the saliva. Incubation periods of this virus may range anywhere between four to eight weeks.

Regarding the typical manifestations of this disease, symptoms can range from fever, fatigue and malaise, sore throat, myalgia and headaches, tonsillitis, cervical lymphadenopathy, acute pharyngitis and oftentimes hepatosplenomegaly. However, younger children are often asymptomatic.

To confirm a diagnosis, a specific heterophile antibody test or otherwise known as the “monospot test” is used, along with a positive serology. The major disadvantage with this method is that it has a high false negative rate due to the delay in antibody production [3]. Serological testing (EBV viral capsid antigen IgM test) proves to be both highly specific and sensitive in the diagnosis of infectious mononucleosis. It is usually performed to not only confirm the diagnosis, but also differentiate between whether the disease is in it’s acute or chronic stages.

Complications are also very rarely seen with a frequency of approximately 1% of individuals with acute EBV primary infections. Of those who do progress with complications, commonly acquire meningencephalitis, haemolytic anaemia and thrombocytopenia [2]. Also mild hepatitis may result but is usually self-limiting.

Turning to treatment, IM is usually a self-limiting viral disease; therefore, supportive treatment is usually the primary choice in the form of fluids, antipyretics, pain medications and rest. [7]. Over recent years there has been progression in the development of a standardised vaccine.

Antiviral drugs such as aiclovir, valaciclovir and ganciclovir have all shown positive results in severe cases of the disease with reducing complications and further reducing the risk of virus shedding from its oropharyngeal repository. [7] Evidence has shown to support the use of corticosteroids in battling sore throat symptoms but as an overall drug in directly suppressing the virus, it has little support. [7]

IM is correlated with other diseases, as its method of progression may be deemed problematic. Diseases such as Hodgkin’s lymphoma, several forms of non-Hodgkin’s lymphoma and nasopharyngeal carcinoma have been related to the chronic pathogenesis of IM. Also, cases of Multiple sclerosis have been linked to cases of infectious mononucleosis; however, the exact pathogenesis behind this is still poorly understood. [4] Chronic fatigue syndrome has been reported in certain cases six-twelve months following the incidence of IM. [6]
AIM

To outline typical and atypical cases of infectious mononucleosis caused by Epstein-Barr virus in children.

OBJECTIVES OF THE STUDY

1. To evaluate the epidemiology of infectious mononucleosis in Lithuania.

2. To review literature regarding clinical features, laboratory findings, modes of diagnostics and methods of treatment of infectious mononucleosis.

3. To discuss complications in various cases of Infectious Mononucleosis.
LITERATURE REVIEW

HISTORY

Filatov recognized the symptoms of infectious mononucleosis as a unique disease (idiopathic adenitis) in the 1880s. The name 'Infectious mononucleosis' was given by Sprunt and Evans in 1920. The virus was isolated from tumor cells in patients with Burkitt’s lymphoma in 1964 by a British pathologist called Epstein (later classified as human herpes virus 4) [2].

CLINICAL FEATURES

Infectious mononucleosis with Epstein-Barr virus (EBV) usually manifests itself asymptptomatically among the younger demographic [8,1]. This is in comparison to obtaining the infection later in life, which usually presents symptomatically. However, when clinical features do appear, they present in the form of fever, fatigue and malaise, sore throat, myalgia and headaches, tonsillitis, cervical lymphadenopathy, and oftentimes splenomegaly [8].

In a recent study where 72 students were analysed for common symptoms of IM, it was found that the most common complaint was ‘sore throat’ occurring in 94% of all subjects. Lymphadenopathy, fatigue, respiratory complaints, headaches, a decreased appetite, fever and lastly, muscle pains then followed this in decreasing order of frequency. Organ enlargement (liver or spleen) was described in less than one-fifth of subjects. Majority of patients with IM describe a sudden onset of sore throat with associated cervical lymphadenopathy. However, others describe a slower progressive onset with a sense of fatigue and muscle aches. In terms of laboratory results, more than three quarters of the subjects had a rise in ALT indicating subclinical hepatitis. [2]

ATYPICAL:

However, atypical presentations have been reported such as haemolytic uremic syndrome. Studies have shown that there was a relation between elevation of EBV markers and this syndrome leading to speculations of correlation between them. This suggests that the virus could have on the pathophysiology in the kidney, as the EBV virus can lead to mucosal inflammation in the glomeruli of the kidney’s parenchyma hence, leading to endothelial cell dysfunction [1]. The 9 year old that was reported in this study presented with an atypical case of HUS that had arisen after his admission to hospital [10]. The titre of the child’s IgM to EBV was significantly raised however no previous E.Coli infection was reported suggesting a possible influence of EBV on setting off the syndrome. This further suggests that EBV may have a roll in causing endothelial cell damage leading to release of certain cytokines and inflammatory mediators incurring in intravascular
coagulopathies. The patient presented with fever, however, no typical diarrhoea was reported preceding hospital admission that is typically seen with E. coli’s Shiga toxin. [1]

Another clinical presentation recorded in studies was Henoch-Schonlein purpura or anaphylactoid purpura, which is a form of small vessel vasculitis that predominates in children [1]. This condition has a higher prevalence in boys and is often preceded by an upper respiratory tract infection and children usually present with a characteristic rash around the buttocks and extensor surfaces of the arms and legs. [11] EBV and HSP have rarely been associated together, as the usual causative agent for the URTI is Group A Streptococcus or other viral causes such as measles, varicella, rubella and hepatitis. [1,12]

A case report reported an 8-year-old boy who presented to the emergency department with multiple purpuric rash and other findings synonymous with HSP such as abdominal pain and elevated white blood cell count. Serologic tests for other possible causative agents along with autoimmune activity came back negative, however, monospot test was positive. [12] Serological test came back with the following results Anti-VCA IgG: positive Anti-VCA: positive, Anti EBNA-1 IgM: negative, Anti EBNA-1 IgG: negative which suggests a primary acute active infection with EBV [13]. This is not the only case where EBV was the primary reason for antibody-associated vasculitis.

A 15-year-old Japanese girl was reported presenting with spots of purpura over her right elbow along with bilateral swollen tonsils and lymphadenopathy in the neck. [14] On admission, her serologic markers were elevated beyond the usual range and after her condition decreased in severity it also showed evidence of past infection of IM.

**TREATMENT**

To treat patients with IM caused by EBV, usually a supportive approach is applied due to the self-limiting nature of the disease [1, 11]. This usually involves the use of analgesics or antipyretics such as acetaminophen to treat the associated fever. Sometimes administrations of IV fluids may be indicated if necessary. Regarding treatment to directly decrease the viral load, there has not been any statistically significant difference in the use of mainstream antiviral agents such as ganciclovir and valganciclovir. In immunosuppressed patients they have been used to treat EBV infections however, their clinical efficacy and safety wasn’t demonstrated through clinical trials [16]. Corticosteroids have also been employed in treating certain inflammatory conditions that can lead to severe compromising of airways. It’s also showed to be useful in treating autoimmune complications such as HUS and TTP but overall, it’s value is shown to be controversial as it’s potential in exacerbating the disease can be problematic. [11,16]

Studies have been performed on whether the need of a vaccine for EBV infections are necessary due to the possible complications, especially those patients who are in immunocompromised states. It can lead to a multitude of epithelial and lymphoid cell malignancies such as Burkitt lymphoma, Hodgkin lymphoma and nasopharyngeal carcinoma [16, 2]. During a study glycoprotein 350 was isolated from the virus and it
succeeded phase 0, and phase 1 clinical trials. Ultimately, a phase 2 double blinded placebo-controlled clinical trial was arranged involving the administration of 50ug of GP350 in 2 groups, 90 individuals in the placebo group and 88 in the vaccine group. [17]

3 doses of the vaccine were administered at various intervals and upon administration of the 2nd dose those; typical clinical features of IM were monitored to see if there was any decrease in incidence of the disease. Positively, incidence in the vaccine group did decrease, however, overall there wasn’t a statistical significant difference between both groups in the study. Future research has been implicated in finding specific surrogate markers in identifying particular carcinomas and lymphomas in order for a possible phase 3 clinical trials to be conducted. [17]

One highly associated disease is tonsillopharyngitis, which is usually caused by Group A Beta-haemolytic Streptococcus [11]. This condition’s most prevalent age group is within the preschool children and it’s very difficult to distinguish between a viral and bacterial cause. Therefore, those patients who develop this condition are treated empirically with penicillin even though the cause of the disease is bacterial only one-third of the time [11]. This antibiotic regime usually consists of the use of penicillin for a minimum of 10 days to eradicate the pathogen entirely, also erythromycin can be utilized if the patient has a known drug allergy to penicillin (i.e. rash). Certain doctors wait for swabs to come back with a positive streptococcal culture but this not always the preferred choice in severe cases of the disease. Practitioners are usually cautious in prescribing amoxicillin due to it’s associated side effect of a widespread maculopapular rash when used in battling tonsillitis caused by IM, and so is hence avoided due to it’s ability in exacerbating the disease. [11]

As a consequence of splenomegaly, children and young adults are heavily advised against any form of contact sports, as the general risk of splenic rupture associated with sport injuries will be significantly increased [1].

**DIAGNOSIS AND LABARATORY FINDINGS:**

When it comes to diagnosing IM, the very first test utilized for screening is the monospot test which is a type of indirect coomb’s test that involves cross reacting the patient’s IgM antibodies with the red blood cells of a horse or sheep [18]. A negative result in the monospot test can also suggest CMV as a possible cause for the IM [18]. Usually those infected with the virus will show positive within 1 week of infection; however, definitive diagnostics for infection with EBV virus can only be performed with the use of serological testing. To summarise diagnosis of EBV infection is primarily made using a combination of clinical features and serological markers such as heterophile antibodies, Anti- VCA antibodies (IgG + IgM) and finally, IgG antibodies to EBNA (nuclear antigen) and EA-D (early antigen diffuse) [13]. Due to the multitude of serological markers that can be tested for, a variety of results can be obtained and each one can be interpreted differently [13]. It is very important to differentiate IM from other diseases such as Hepatitis, lymphoma, pancreas carcinoma, SLE, malaria, and infection with rubella or
parvovirus as these conditions can sometimes lead to false positive results. If it is tedious to perform serology, then PCR can be used instead [24].

*Table 1. Classification of stages of EBV infection according to serological markers and heterophile antibody testing.* [13, 1, 2, 19]

<table>
<thead>
<tr>
<th>Clinical status</th>
<th>Heterophile Antibody</th>
<th>EBV Specific Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>VCA-IgM</td>
</tr>
<tr>
<td>Susceptible</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acute Primary Infection</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chronic primary infection</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Past infection</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reactivation</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

There are various advantages and disadvantages with using different techniques in detecting antibodies against EBV. The most accepted option is the heterophile antibody test due to its ease in use, cost and a relatively low rate of false positives. [2] As stated in the table above, various antibodies can be used to distinguish between stages of infection. EBNA IgG antibody in particular is very specific in determining whether the patient has an acute infection or is in convalescence. The most accurate and efficient method of staging the infection would be using immunoblot antibodies but are not usually indicated due to the expense of performing it routinely.
Histological findings of a patient with IM would show atypical mononuclear lymphocytes in the blood and T-cell hyperplasia in the paracortex of lymphatic nodes. In a study conducted in Japan to assess the potential of EBV causing lymphoproliferative disease in children and adolescents, it was found that a minority of these patients suffering from tonsillitis showed characteristics of EBV infection. Tonsillectomies were performed on this sample population and it showed that from the total 630 specimens gathered, 14 showed lesions positive with EBV encoded small RNA and consequent development of hyperplastic germinal centres of lymph nodes with non distinct defined borders or otherwise ‘pale clear zones’. This raises the query of screening those patients in the younger demographic for EBV-associated LPD and not just the older demographic in immunocompromised states. [12] Blood viral load is highly suggested in screening of immunocompromised patients susceptible to EBV infection. This can usually be done by PCR and is vital as it can change the outcome of management. [2]

A case report of a 3-year-old child who was admitted to hospital with a supposed typical picture of lymphoprolifertive disease was assessed. She presented with enlarged bilateral pharyngeal tonsils and submandibular lymphadenopathy and hepatosplenomegaly. Suspicion to whether or not this patient had an adequate antiviral immune response was questioned so a screening for immunodeficiency was therefore performed with no positive results. This picture can be usually associated with a coinfection of CMV and EBV, which can occur in immunocompetant patients and this can elicit a great response in reactive CD8+ cells. This patient, however, showed no positive serological results corresponding with CMV infection, but a positive PCR for EBV load was found. Immunophenotyping of the blood lymphocytes was also performed demonstrating a predominant CD8+ T- cell presence along with a leucocytosis, 83% of which were atypical lymphocytes.
Consequently, this patient was diagnosed with infectious mononucleosis with no lymphoproliferative disease [22]. An extremely rare complication of EBV infection is Haemophagocytic Lymphohistiocytosis (HLH) and this is an over aggressive inflammatory response primarily cause by EBV [23]. The patient above did not meet the minimum number of diagnostic criteria outlined for this condition but this does not rule out the necessity to screen for this possible complication as a cause for her reaction.

**COMPLICATIONS:**

Infectious mononucleosis is associated with a numerous set of complications and these can be sub classified into: acute, long-term and extremely rare.

**Complications of acute illness:**

During the acute phase of the disease, life- threatening complications are hardly ever reported. Approximately 1% of patients with IM report with complications and are usually tonsillopharyngitis, haemolytic anaemia, thrombocytopenia airways obstruction due to inflammation and meningoencephalitis. [2] Splenic rupture is a well-documented and weary complication that physicians always make patients aware of.

**Splenic rupture**

Splenic rupture is reported in less than 1% of cases. This usually occurs with patients who do not avoid contact sports over a period of 3 weeks when first diagnosed. During this period, minimal contact of the enlarged spleen can have a high mortality rate. [2] Spontaneous rupture is not very common (0.1-0.5% of IM cases) and certain cases revealed rupture occurring even up to 7 weeks after initial diagnosis. [47] Conservative treatment is indicated in most cases where patients are stable and operative intervention with splenectomy in not commonly performed [47]

**Respiratory complications**

IM can oftentimes lead to compromising of the airways. This atypical manifestation of the disease is seen more when it affects the Waldeyer’s ring. This involvement should be suspected in any patient that has difficulty swallowing, deterioration in respiratory function or enlargement of the lymph nodes [42]. Only in cases where the patient’s airway becomes obstructed should intervention with assisted ventilation or corticosteroid be implicated.

Pneumonia is a very rare complication of EBV primary infection and has only been reported 5 times in case reports. Out of the 5, 3 were confirmed in having a form of interstitial pneumonia complicated by respiratory insufficiency while the other 2 cases were lower lobe consolidation and plueropneumonia. However, due to the rarity of pneumonia witnessed in the context of IM, it is hard to determine the exact pathophysiology leading to the infection. Due to the immunosuppressive nature of EBV infecting T lymphocytes, it can
be suspected that this is how children become more susceptible to a pulmonary infection [43].

**Pharyngitis**

Pharyngitis is heavily associated with EBV and can progress to the exudative subtype in 1 of every 3 of patients. Coinfection is usually caused by group A- Streptococcus. As already mentioned, pharyngitis with tonsillar involvement can become very dangerous as this can lead to fatal airway obstruction. Intubation and admission to intensive care may be needed. [2, 47]

**EBV – induced encephalitis**

Encephalitis exhibited solely due to infection with EBV is rarely ever fatal (0.1-1% of cases) [45]. However, the incidence of the overall disease increases by almost 6% (0.5 to 7.3) when patients are admitted with IM [44]. The most common symptoms witnessed with these patients are focal neurological symptoms, epilepsy, disorientation, and in extreme cases, comatose. It is hard to determine the exact pathogenesis of this form encephalitis, however, symptoms are usually more apparent when there is an absence of IM symptoms. Also, severity is heavily location dependent. Involvement of the brain stem can lead to a worse prognosis and higher rates of mortality [46].

**Long-term complications:**

Complications such as Hodgkin’s lymphoma and multiple sclerosis have been associated with primary EBV infection. The link between these diseases is not fully understood but individuals with a genetic predisposition, various ethnicities and exposure to environmental factors appear to be more susceptible.

**Burkitt Lymphoma**

IM is usually a benign condition that is self-limiting in nature and rarely progresses with complications [1]. When it does produce complications, it can result in an array of conditions, one of those being Burkitt’s lymphoma. [18] This is a neoplastic growth, in specific B-cell, which usually arises in children and young adults in the form of an extra nodal mass. It has two forms, Endemic form and Sporadic, usually involving the jawbones and abdomen, respectively. [18] The pathogenesis of the lymphoma usually involves a translocation mutation of chromosome 8 to chromosome 14 leading to an over activation of a specific oncogene, c-myc [18, 1]. A study showed that the endemic form of the lymphoma is highly associated with EBV (85%) as opposed to the sporadic form (10-15%), and is especially prevalent among Africa and South American regions. [26] A cohort study has shown that depending on the location of the extra nodal mass, a level of prognosis can be anticipated. A study period from 2003 to 2011 in Kenyan children showed that 63% of them with jaw tumours and 33% with abdominal tumours survived using chemotherapy based treatments. [25] Imaging is vital in determining the pathology. For head and neck
involvement, MRI is usually utilized. [26] It is important in accessing Waldeyer ring involvement and bone destruction, and lastly to determine the staging of the disease. [27] Since EBV-associated endemic Burkitt lymphoma is characterized as a high-grade cancer, therefore treatment involves a combination of drugs, rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone, otherwise known as the ‘R-CHOP’ regimen. [24]

**Multiply Sclerosis**

A study was conducted in central England to prove if being previously infected with IM indeed increases the risk of obtaining MS. The outcome was that there was a significant correlation between the diagnoses of MS at an interval of 10 year post-IM infection. Another study further reaffirmed this stating that the most significant antibody found among MS patients who previously were infected with IM was EBNA-1. Overall, the work of more than 11 studies concluded that there is an increased seroprevalence of EBV in patients with MS in comparison to the controls. [41] The exact physiology as to why this may be the case is not yet fully understood but theories suggest that EBV plays an early role in the activation of autoreactive T-Lymphocytes. This in turn can stimulate a cascade of inflammatory responses leading to demyelination and depletion in axons. Another hypothesis for this that was suggested is hygiene theory. This states that in the developed world, due to the fact that we are in less contact with pathogens, therefore this can lead to our own body’s immune system forming autoimmunity. Especially in elder patients who presented with EBV, this may very well be the case. However, EBV is associated with the early development of MS and therefore, unlikely to cause reactivation of an already latent MS. [40,1]

**Extremely rare complications:**

Peculiar and extremely rare complications such as Alice in Wonderland syndrome and Haemophagocytic lymphohistiocytosis have been associated with EBV primary infection. The rarity of both diseases supports further research and not much is known about each disease. Acute kidney injury secondary to an EBV infection has even been reported.

**Alice in Wonderland Syndrome**

Alice in wonderland syndrome, also known, as dysmetropsia is a rare complication of children infected with EBV. It is described as a perceptual disorder where individuals experience illusions such as distortions in shape and size of the person’s own dimensions and body position. It is a very peculiar disorder where individuals also describe a sense of detachment from their own thoughts or dissociation from the reality of the outside world.
Out of these subtypes of the pathology the majority of patients describe visual symptoms similar to that in type B at around 75% of total cases [28]. Cases of this syndrome are oftentimes quite difficult to diagnose due to sheer variability between every individual’s symptoms. However, an English psychiatrist known as John Todd developed his own criteria in diagnosing the condition, but it is usually a diagnosis of exclusion. The role of EBV in causing AIWS is not very well understood but certain theories suggest a damage to lower cortices, in specific the temporooccipital junction. [29] The method by which it causes damage is very speculative but reports have shown that infection with EBV can show a dampening in EEG impulses in the occipitoparietal area of the brain, disruption in electrical conductance and small epileptiform like seizure activity. [28] This is the area where somatosensory relays with visual information to give a perception of an individuals own appearance. 166 cases of AIWS were analysed to see what was the most common causes of the symptoms and infections amounted to 22.9%, where EBV was reported to have caused the clear majority with 15.7%. [29] As of now there is no treatment for this condition due to scarcity of medical data as only 170 cases were recorded up to 2016.

**Haemophagocytic lymphohistocytosis (HLH)**

HLH, also known as haemophagocytic syndrome is an extremely rare condition, which physicians may never see in their lifetime and it is oftentimes difficult to diagnose. This pathology can be subdivided into primary, which is usually associated with a genetic pathology, and secondary which is an acquired form of the disease. In regards to the secondary subtype, EBV is the leading causative factor along with HIV and CMV which can all stimulate an unregulated over activity of macrophages in the immune system. [30] Due to the absolute rarity of the condition, its clinical features can be sometimes misinterpreted for a malignancy with a fever, splenic enlargement, cytopenias and a decrease of Natural Killer- cell activity. Etoposide, a chemotherapy agent, has shown to be beneficial in treating HLH caused by EBV and is therefore indicated. [31] A cohort study during the period of 2003- 2005 was conducted in European children where 10 cases of EBV driven HLH were analysed. The conclusion of the study was that molecular diagnosis should be heavily stressed upon. Quantifying the EBV load in cases of HLH is important in

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**Table 2. Proposed classification of symptoms experienced in Alice in Wonderland Syndrome.** [28]

<table>
<thead>
<tr>
<th>Types</th>
<th>Obligatory symptoms</th>
<th>Facultative symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</td>
<td>Aschematia; partial or total macrosomatognosia or microsomatognosia; paraschematia</td>
<td>Derealization, depersonalization, somatopsychic duality, aberration in judgement of time</td>
</tr>
<tr>
<td>Type B</td>
<td>Macro- and micropsia and/or tele- and pelopsia. When micropsia and telopsia appear at the same time and for the same object: porropsia Lilliputianism (people appearing smaller)</td>
<td></td>
</tr>
<tr>
<td>Type C</td>
<td>Type A + type B symptoms</td>
<td></td>
</tr>
</tbody>
</table>

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further research of the condition in order to diagnose future EBV-associated cases and to better treatment regimes. [32]

**Acute kidney injury (AKI)**

One case report presented with a 13 month old boy who had a 4 day history of high fever (40 degrees) and rash. He had a recent history of URTI, which he was treated with clauvanic acid and amoxicillin, however, the symptoms mentioned above persisted. His physical examination revealed no other symptoms or signs. His rash was localized to the lower limbs. The laboratory findings showed an atypical lymphocyte count of greater than 10%. On the fourth day of hospitalization, the laboratory tests were repeated due to periorbital oedema and a decreasing urine output. Due to the deterioration in kidney function, an ultrasound was indicted which found enlargement in both kidneys and free fluid collections in various sites of the abdomen (perihepatic and perisplenic). Initial treatment was indicated with restriction of fluids along with boluses of calcium gluconate and sodium bicarbonate. Later, serology was performed and the boy’s results came back positive for EBV VCA IgG and EBV VCA IgM thus indicating an acute infection of EBV. The patient developed oliguria and was transferred to a dialysis unit. A renal biopsy showed results of interstitial inflammatory changes with T cell and histocyte infiltration. About one month after admission after periodic dialysis, the patient’s kidney function began to recover and was ultimately diagnosed with an AKI with metabolic acidosis secondary to an atypical presentation of EBV infection. [48] The most commonly seen cause for renal dysfunction among EBV infections is interstitial nephritis, however, rhabdomyolysis is also quite common. Symptoms such as haematuria (2% of IM cases) and proteinuria (18% of IM cases) have been reported in literature quite often, while azotaemia has been sparingly mentioned (8 case reports). [42]
EPIDEMIOLOGY

Using ULAC which is the Lithuanian database for Infectious Diseases and AIDS Center, information was gathered from tables to create a number of charts which all report the prevalence of infectious mononucleosis in children depending on “gender”, “age” and “area of living”. The purpose of this retrospective study was to see if there was a high prevalence of IM among children in Lithuania and also comparing it to other countries. The null hypothesis in this study was that there is no significant relationship between Lithuania’s rate of IM in comparison to other countries, where as the alternate hypothesis states there is some association between them.

In a retrospective study among a population of Chinese children in Renmin hospital, Shiyan, it was found that out of the 253 patients who were primarily infected with EBV under the age of 15, the majority were under the age of 4 years (74.7%). In terms of gender distribution it was found that 60% of those children infected were male. This study concluded that among that the age group most susceptible to EBV infection were those children between the ages of 6months and 1yrs old. [33] In contrast to the prevalence of EBV infections among children in Lithuania, the number of reported cases in this study is experiencing a gradual increase over a period of 4 years. [33]

![Fig. 1. Age distribution of patients infected with EBV from 2014 to 2017 in Renmin Hospital, China.](image)

In another study conducted in Northern China, a similar result was obtained where the ratio of male to female cases were 1.4:1. However, the majority of patients in this study were within the age demographic of greater than 6 years old (50.7%) [34].

In Grenoble University hospital, France, a retrospective study has shown that in regards to primary infection of EBV, there was a peak in the 2- 4 years age group among children. [36]
A US study conducted on an age group of between 6-19 year olds and also accounted for external factors that might influence acquisition of the virus. Their results showed that the highest percentage of seroprevalence was among the 18-19 years old age group (89%) and the lowest among the 6-8 years old (50%). [37]

A large-scale study of seroprevalence of EBV among various regions in Taiwan produced very interesting results. As this was just testing the prevalence of EBV among age-stratified groups, it doesn’t necessarily mean they were experiencing an active infection. This study, which used the data of 3552 blood samples, concluded that the highest seroprevalence recorded was that among the 0-5 age cohort at 89.9% [35]. The importance of this study was to emphasise the future research in producing a vaccine against EBV in order to decrease the recurrence rate.

In one study in Poland, the highest rate of primary infection was among the 1 to 5 years old age group (62% of total reported cases). [39]
RESEARCH METHODS AND METHODOLOGY

In order to fulfill the objectives outlined in my Literature review, multiple research databases were utilized including PubMed, UptoDate, and Blood Journal. A range of search terms were used to make the primary search including “Infectious Mononucleosis”, “Epstein barr virus”, “EBV”, “Kissing disease”, and “Glandular fever”. These were then put into an advanced search engine to include other relevant terms such as “Children”, “Peculiarities”, “Characteristics” and then number of articles were obtained.

An initial review of these articles was performed on the basis of ‘year of publication’, ‘the abstract’s content’ and ‘title’. Articles with publications following the year of 2003 were selected in order to avoid the possibility of outdated information. After extensive reviewing, a number of articles were deemed appropriate to be included in the literature review. The final step was to assess the relevance of the topic to the specific objective, thus this was where the articles were fully assessed and relevant information was extracted. [Fig 2]

The epidemiologic data of infectious mononucleosis in Lithuania was collected using ULAC basis of medical statistics for the last 5 years and organized into tables. Microsoft excel 2010 was used to create tables of data, which were then further categorized on the basis of “gender”, “age” and “area of living”. The two major age groups were those between 0-9, and 10-17. Locality was split depending on the children living in rural or metropolitan areas. These tables were then input into multiple charts to be displayed.
Fig 2. Literature review methodology.

PUB MED

- Papers that were reviewed after initial search: (1024)
- Papers deemed appropriate after thorough reading of abstract: (122)
- Papers considered eligible after full article has been assessed: (64)

OTHER

- Papers that were reviewed after initial search: (35)
- Papers deemed appropriate after thorough reading of abstract and summaries: (20)
- Papers considered eligible after full article has been assessed: (18)

Total number of articles and scientific reviews included in the studies = (48)
## RESULTS

*Table 3. Summary of articles used in the Literature review.*

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Disease/Topic</th>
<th>Age</th>
<th>Gender</th>
<th>Type of Study</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fallahzadeh, Mohammad Amin [10]</td>
<td>Hemolytic uremic syndrome</td>
<td>9 year old</td>
<td>Male</td>
<td>Case Report</td>
<td>EBV associated HUS doesn’t always have typical symptoms such as absence of oliguria, hypertension and edema.</td>
</tr>
<tr>
<td>2</td>
<td>Burcu Karakayali [12]</td>
<td>Henoch Schonlein purpura</td>
<td>8 year old</td>
<td>Female</td>
<td>Case report</td>
<td>EBV can be an etiological factor for HSP vasculitis and other autoimmune conditions.</td>
</tr>
<tr>
<td>3</td>
<td>Yamaguchi M [14]</td>
<td>Henoch Schonlein purpura</td>
<td>15 year old</td>
<td>Female</td>
<td>Case report</td>
<td>EBV can stimulate ANCA- associated vasculitis.</td>
</tr>
<tr>
<td>4</td>
<td>Cohen, Jeffrey I [17]</td>
<td>Vaccine development</td>
<td>Multiple age groups</td>
<td>Male and Female</td>
<td>Double blinded study</td>
<td>Incidence of IM decrease in the vaccine group in phase 2 trials.</td>
</tr>
<tr>
<td>5</td>
<td>Klutts, J S et al [13]</td>
<td>Serology testing</td>
<td>Multiple age groups</td>
<td>Male and Female</td>
<td></td>
<td>Recommend using all five-antibody titres when diagnosing a primary acute infection. EBV VCA IgM, IgG and heterophile</td>
</tr>
<tr>
<td>No.</td>
<td>Author(s)</td>
<td>Condition</td>
<td>Age</td>
<td>Gender</td>
<td>Source type</td>
<td>Description</td>
</tr>
<tr>
<td>-----</td>
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</tr>
<tr>
<td>6.</td>
<td>Krupka, Joanna Alicja [22]</td>
<td>IM with suspected HLH</td>
<td>3 year old</td>
<td>Female</td>
<td>Case report</td>
<td>Very difficult to diagnose children of various age groups.</td>
</tr>
<tr>
<td>7.</td>
<td>Nicholas John Bennett [47]</td>
<td>Splenic Rupture</td>
<td>All ages</td>
<td>Male and female</td>
<td>Article</td>
<td>Splenic rupture is a rare complication but can be fatal.</td>
</tr>
<tr>
<td>8.</td>
<td>Vasileios Bolis [42]</td>
<td>Upper airway obstruction</td>
<td>Not mentioned</td>
<td>Male and Female</td>
<td>Literature review</td>
<td>Any diagnosed IM patient with dysphagia or experience respiratory distress should be suspected with Airway obstruction.</td>
</tr>
<tr>
<td>9.</td>
<td>Vasileios Bolis [42]</td>
<td>Pneumonia</td>
<td>Not mentioned</td>
<td>Male and Female</td>
<td>Literature review</td>
<td>Immunosuppressive nature of EBV can increase the chance of IM patients acquiring temporary respiratory infections.</td>
</tr>
<tr>
<td>10.</td>
<td>Nicholas John Bennett [47]</td>
<td>Pharyngitis</td>
<td>Not mentioned</td>
<td>Male and female</td>
<td>Article</td>
<td>Tonsillitis along with pharyngitis can lead to airway obstruction.</td>
</tr>
<tr>
<td></td>
<td>Author(s)</td>
<td>Condition</td>
<td>Age Groups</td>
<td>Gender</td>
<td>Study Type</td>
<td>Results</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>11</td>
<td>K. Abul-Kasim [46]</td>
<td>EBV induced encephalitis</td>
<td>Multiple age groups</td>
<td>Male and Female</td>
<td>Case report + Literature review</td>
<td>EBV localised to brainstem have the highest mortality rate and locating the involvement of EBV in the brain can aid in determining prognosis.</td>
</tr>
<tr>
<td>12</td>
<td>Doja A [44]</td>
<td>EBV induced encephalitis</td>
<td>3-17 years old</td>
<td>Male and Female</td>
<td>Retrospective study</td>
<td>21 of 216 (6%) patients diagnosed with encephalitis had evidence of EBV. Of those only 1 had typical symptoms of IM beforehand.</td>
</tr>
<tr>
<td>13</td>
<td>Buckle G [25]</td>
<td>Burkitt’s lymphoma</td>
<td>Multiple age groups</td>
<td>Male and Female</td>
<td>Cohort study</td>
<td>EBV load in patients diagnosed with Burkitt’s lymphoma did not alter staging or prognosis.</td>
</tr>
<tr>
<td>14</td>
<td>Kaymaz Y [26]</td>
<td>Burkitt’s lymphoma</td>
<td>2 - 14 years old</td>
<td>Male and Female</td>
<td>Retrospective study</td>
<td>EBV type 1 stimulates the formation of Burkitt’s lymphoma without the need for genetic predisposition.</td>
</tr>
<tr>
<td>15</td>
<td>Derinkuyu BE [27]</td>
<td>Burkitt’s Lymphoma</td>
<td>Multiple ages, children (&lt;15)</td>
<td>Male and Female</td>
<td>Pictorial review</td>
<td>Radiologic testing is necessary in diagnosing Burkitt’s lymphoma and late detection may lead to a worse prognosis.</td>
</tr>
<tr>
<td>16</td>
<td>Virtanen JO, Jacobson S [41]</td>
<td>Multiple sclerosis</td>
<td>Multiple age groups</td>
<td>Male and Female</td>
<td>Literature review</td>
<td>In all studies review percentages of patients with evidence of EBV were higher in MS groups than the control groups. However, only in plasma DNA, peripheral blood mononuclear cells DNA and Brain DNA. CSF DNA showed no statistical difference.</td>
</tr>
<tr>
<td>17</td>
<td>Goldacre MJ [40]</td>
<td>Multiple sclerosis</td>
<td>Multiple age groups</td>
<td>Male and Female</td>
<td>Record-linkage study</td>
<td>14 years was the mean time among a cohort from admission with IM to diagnosis of MS in preselected patients.</td>
</tr>
<tr>
<td>No.</td>
<td>Authors</td>
<td>Disease</td>
<td>Age</td>
<td>Gender</td>
<td>Methodology</td>
<td>Findings</td>
</tr>
<tr>
<td>-----</td>
<td>--------------------------</td>
<td>----------------------------------------------</td>
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<td>--------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>18</td>
<td>Mastria G, Mancini V, Viganò A, Di Piero V [28]</td>
<td>Alice in Wonderland syndrome</td>
<td>Multiple ages.</td>
<td>Male and Female</td>
<td>Literature review</td>
<td>Diagnosing AIWS can be difficult due to variability in reported cases even with criteria. (dyschromatopsia, entomopia, mosaic vision, palinopsia, polyopia etc.)</td>
</tr>
<tr>
<td>19</td>
<td>Brumm K, Walenski M [29]</td>
<td>Alice in Wonderland syndrome</td>
<td>12 years old</td>
<td>Male</td>
<td>Case study</td>
<td>With regards to micropsia there was a noted decrease in activity in the primary cortices and an over-activity in extra-striatal regions in viral-induced AIWS.</td>
</tr>
<tr>
<td>20</td>
<td>Thomas W, Veer MV [30]</td>
<td>Haemophagocytic lymphohistiocytosis (HLH)</td>
<td>Multiple age groups</td>
<td>Male and Female</td>
<td>Literature Review</td>
<td>HLH should be suspected in ill patients following an EBV with raised ferritin levels, cytopenias and who exhibit unexplained fevers.</td>
</tr>
<tr>
<td>21</td>
<td>Imashuku S. Kuriyama K. Sakai R [31]</td>
<td>Haemophagocytic lymphohistiocytosis (HLH)</td>
<td>Multiple age groups</td>
<td>Male and Female</td>
<td>Literature Review</td>
<td>When patients are identified as ‘high-risk’ or resistant to conservative treatment, a 4 week course of etoposide should be implemented.</td>
</tr>
</tbody>
</table>
From the 23 various types of studies summarised in the above table: 18 were used to evaluate complications, 3 were used to evaluate atypical cases of infectious mononucleosis and 2 were used to represent different diagnostic methods and future in vaccine development.

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Study Authors</th>
<th>Study Title</th>
<th>Age and Gender</th>
<th>Study Type</th>
<th>EBV Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>Hans-Joachim S. Wagner et al [32]</td>
<td>Haemophagocytic lymphohistiocytosis (HLH)</td>
<td>2–14 years old, Male and Female</td>
<td>Retrospective study</td>
<td>EBV- viral load analysis is key in diagnosing EBD associated HLH and can be used to monitor the disease.</td>
</tr>
<tr>
<td>23</td>
<td>Gamze Ozgurhan, Mustafa Ozcetin [48]</td>
<td>Acute kidney injury (AKI)</td>
<td>13 months old, Male</td>
<td>Case Study</td>
<td>EBV acquired early in childhood can lead to deterioration in kidney function and renal biopsies can aid in confirmatory diagnoses.</td>
</tr>
</tbody>
</table>
In total, 1507 children until 18 years of age were diagnosed with IM in accordance with ULAC basis of medical statistics from 2014 - 2018. Concerning the study of IM in Lithuania, recent statistics have revealed that the total number of males that were diagnosed with IM was 828 reported and as for females were 679 (boys: girls ratio 1.22:1). Therefore 54.94% (fig. 2) of the total reported cases recorded over the previous 5 years were male (CI 95%, P<0.05).

Fig 3. Sex distribution of children diagnosed with IM from the years 2014-2018 in Lithuania.

There was a general decrease in the number of reported cases of IM among males from the period of 2014 - 2018. In contrast, among females there was a rise from 132 in 2014, to 145 cases in 2015 and also from 137 in 2016, to 153 in 2017.

Over the 5 years period that was studied, the highest prevalence of IM was the 0-9 years old age group. From the 1507 reported cases of IM, 1107 were in the age group of 0-9 years old (73.5%) and the rest (400) were in the 10-17 years age group (26.5%).

Overall, the number of cases reported among children living in rural areas (292) is much less than what is reported in metropolitan areas (1215). This can be attributed to a scarcity of health care services or an inability of rural dwellers to access hospital services in order to confirm diagnosis. It is difficult to assume that there is just a lesser incidence of IM in
rural areas among children due to other already mentioned external factors.

**Fig 4. Number of boys with IM till 9 years of age living in metropolitan areas in Lithuania 2014-2018.**

**Fig. 5. Number of girls with IM till 9 years of age living in metropolitan areas in Lithuania 2014-2018.**

Comparing fig.4 and fig.5 the incidence of IM between boys and girls in the age group of 0-9 living in city areas, it can be seen that there is a higher prevalence among boys (530)
than girls (359). Regarding the number of cases over the years it shows that there is a gradual decrease in the number of cases between both genders from 2014 till 2018, 111 to 96, and 72 to 64, respectively.

**Fig 6. Number of boys diagnosed with IM between the ages of 10-17 living in metropolitan areas in Lithuania 2014-2018.**

**Fig 7. Number of girls diagnosed with IM between the ages of 10-17 living in metropolitan areas in Lithuania 2014-2018.**
Turning to the older cohort with teenagers between the ages of 10-17, there is a similar phenomenon within the male population showing a rather consistent trend throughout the year. Girls aged between 10-17 living in cities have a higher incidence of IM (186) in comparison to their male counterparts (140) as is documented over the 5-year period. In totality, the amount of cases reported among the 10-17 cohort (326) is significantly less to that of the 0-9 age group (889) living in metropolitan areas. [Fig6, Fig7]

Fig 8. Number of boys diagnosed with IM until 9 years of age living in rural areas in Lithuania 2014-2018.
Fig 9. Number of girls diagnosed with IM until 9 years of age living in rural areas in Lithuania 2014-2018.

There is a sharp decrease in the number of cases of IM among boys living in metropolitan areas (530) in comparison to those living in rural areas (134) within the same 0-9 age group [fig4, fig8]. The data reveals that the female population within this demographic has quite a significant number of months throughout the year with almost no occurrences of IM [fig9].

Fig 10. Number of boys diagnosed with IM between the ages of 10-17 living in rural areas in Lithuania 2014-2018.
Fig 11. Number of girls diagnosed with IM between the ages of 10-17 living in rural areas in Lithuania 2014-2018.

Similarly in both fig 10 and fig 11 the diagnosis of IM is practically a rarity with the number of reported cases hardly ever reaching an excess of 2 patients on any given month. In rural areas, girls between the ages of 10-17 feature a higher incidence of IM (50), which is more than double that of boys (24).
DISCUSSION

Epidemiology aspects

Primary EBV infections are usually asymptomatic or can present with nonspecific symptoms such as (fever of unknown origin). Therefore it is not easy to evaluate epidemiological data of IM.

In regards to the comparison of the prevalence of IM within children in Lithuania to the population of Chinese children in Renmin hospital, Shiyan, it can be said that they share a similar gender distribution of boys to girls (ratio 3:2) [33]. Also, there was a higher incidence in younger children (<4 years), similar to that of in Lithuania. In Northern China, this gender distribution (1.4:1) was different to that of Lithuania (1.22:1).

Grenoble hospital in France has a similar incidence to Renmin hospital, which further supports the claim of a higher incidence of IM among toddlers. Studies in Poland revealed similar results also. A study gathered in U.S.A juxtaposed these results by asserting that the predominant cases of IM were between 18-19 years old age cohorts. However, children under the age of 6 weren’t accounted for so it is difficult to evaluate the exact outcomes of all age groups. In Taiwan, progressive measures have been made concerning the advancement of a potential vaccine. This was attested for by showing results of highest seroprevalence among children less than 5 years old. Studies in Lithuania have revealed similar results concerning IM patients ages less than 9 years old. A study in Poland revealed that the majority of reported cases of IM were among the 1-5 year old age group, similar to that among Lithuanian children.

Studies in countries such as China, France, Taiwan and Poland showed similarities in sex distribution while others such as USA showed differences with a predominantly higher age group of primary infection.

Over recent years the number of reported cases of infection by EBV have increased in various countries [2]. The age group of children under the age of 10 years old are particularly vulnerable to infection. In our study of Lithuanian children, we found that cases of IM decrease with a proportionate increase in age (only 26.5% of diagnosed cases were in the 10-17 age range).

The real challenge with EBV is with its ever-growing seroprevalence [2]. It can also prove to be advantageous as more atypical cases are being reported which can lead to better treatment regimens.

General aspects

Literature suggests that clinical features vary on a case-to-case basis of IM. There isn’t a defining set of symptoms that pertain to the disease [2]. It is not fully understood why older individuals report more symptomatic cases as opposed to children [2]. However,
certain case reports have made a progression in understanding a link between the disease onset and associated symptoms. For example, HUS and primary EBV infection. The atypical presentations provide an insight into understanding the correlation between the virus and other symptoms. [10]

Conflicting opinions of physicians have suggested that not having a specific treatment for the disease may seem problematic. However, due to the fact that the vast majority of IM cases present itself asymptotically, there may not need to be a form of specified treatment. Conservative treatment is sufficient in most cases; however, patients in immunodeficient states require a more specified form of treatment. Treatment of autoimmune and inflammatory conditions stemming from EBV infections continues to be debatable by most physicians.

Further research into developing a universally recognized vaccine is important. Due to the high prevalence among young children and certain dangerous complications that can occur late in life, a vaccine may be necessary. Isolating and producing vaccines specifically towards gp350 protein may not be the best means forward, as the potentiation of EBV in gaining access through other proteins is quite high. Including other proteins may potentially help the efficacy of the vaccine trials. [2] Nonetheless, producing a vaccine seems a high priority of many researchers as the reported cases of EBV-induced malignancies increases.

The complications outlined above are rarely fatal and the likelihood of patients developing them are slim. However, certain ones can be acute in their nature of onset such as airway obstruction due to laryngeal edema and splenic rupture. Others have a more a gradual onset if they arise such as HLH, AIWS and EBV-induced encephalitis, whereas other may take years like Burkitt’s lymphohoma and multiple sclerosis. Physicians should be weary about the atypical manifestations seen with IM and pay particular attention to abnormal clinical features and unresolved laboratory findings. Raising awareness about these complications and others that aren’t mentioned above such as hepatitis, cholecystitis, myocarditis, artherosclerosis etc. may aid physicians in providing more focused care towards children suffering with IM. As with the majority of these conditions the pathophysiology can be associated with the immunosuppressive nature of EBV, but the exact patterns are not fully understood so further research is needed. Also, an influential factor in the outcomes of these complications is the immunodeficiency status of the patient. For example, lymphomas associated with EBV are much more common in patients who had just undergone organ transplantations due to the suppression of the immune system post operation. [47]

A greater understanding between the mechanisms and these atypical manifestations will serve valuable in mitigating the morbidity rate caused by them. The real challenge with EBV is with its ever-growing seroprevalence. It can prove to be also advantageous as more atypical cases are being reported which can lead to better treatment regimes.
CONCLUSION

In summary, clinical features vary from case to case of IM. There are many different studies, which demonstrate various features associated with infectious mononucleosis.

1. The incidence of IM in Lithuania is higher among boys then girls (54.94% of boys) (ratio 1.22:1 boys: girls) and among the younger children (less than 9 yrs. old).

2. Literature revealed that most common clinical features in IM are sore throat, lymphadenopathy and fatigue. Treatment for infectious mononucleosis in most cases is conservative, while glucocorticoids are reserved for those who have a degree of airway compromise. Diagnosis can be usually confirmed with a combination of serological tests. Further research into vaccine development may serve as the future in decreasing complications associated with EBV.

3. Literature showed that complications could be further categorized according to their disease course (acute, long-term) and rarity. A multitude of complications also revealed a possible pathophysiological development leading from EBV (e.g splenic rupture, encephalitis, pharyngitis, respiratory obstruction, Burkitt lymphoma) while others are not yet fully understood (Alice in Wonderland syndrome, multiple sclerosis, acute kidney injury). Atypical cases of EBV and hemolytic uremic syndrome and Henoch-Schönlein purpura have been reported.
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