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Ear, nose and throat manifestation of viral systemic infections in pediatric patients

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ABSTRACT

Objective/Methods: An exhaustive review of literature was performed to investigate available data and evidences regarding pediatric otolaryngologic manifestations of viral systemic infections.
Results/Conclusions: Modern otolaryngologists should be familiar with viral systemic infections since many have head and neck manifestations. Cooperation between otolaryngologist, paediatrician and virologist can be considered and excellent tool in diagnosis and treatment of these diseases in particular when complications occur.

Contents

1. Introduction

There are multiple systematic viral infections that can manifest themselves in ORL related organs. Their actions can work directly or indirectly causing an alteration in the human immune system and a consequent secondary bacterial invasion. Notable advances in the diagnosis and treatment of viral infections have been mitigated by the appearance of new pathological processes, for example AIDS, which often has its initial manifestations in ORL regions. Table 1 is a list of illnesses affecting different anatomical sites and the viral etiologies that commonly strike each particular location.

Considering the vast nature of the subject, we subdivided our treatment into three parts corresponding to the same groups of interrelated viral illnesses:

- Viruses that can cause deafness.
- Viruses that can cause inflammation in the upper respiratory tract.
- Viruses particularly relevant to ENT (infectious mononucleosis, papillomatosis, herpes infections).

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Ascertaining specific viral causes of most infections is neither necessary nor cost-effective, and should be reserved only for specific cases. Clinical and epidemiological acumen remain the basis for a presumptive diagnosis. When a specific diagnosis is necessary, diagnostic procedures based on biochemical and molecular biological processes provide sensitive, specific and rapid results [1].

In most viral infections, immunity to re-infection generally lasts a short period of time due to the host's limited immunological response or, rather for an antigenic change in the virus.

2. Viral illnesses which cause deafness

Viral pathologies that can cause deafness can be congenital, appear in either the pre-natal or postnatal period and can also be acquired upon contact with the pathogen [2–4] (Table 2).

In particular, the hearing damage caused by congenital infections can be part of a severe syndrome (such as "congenital rubella syndrome") but more frequently it is the first and only manifestation of intrauterine infection. Common childhood viral infections, such as measles and mumps are probably an unrecognized cause of acute or progressive damage to hearing [5].

Table 1
Viruses and syndromes in childhood

Pathology	Virus
RHINITIS	Adenovirus – Coronavirus – Parainfluenza viruses – Rhinovirus
STOMATITIS	EBV – Herpes simplex
PHARYNGITIS	Adenovirus- Coxsackie A – Parainfluenza viruses – Enterovirus-echo – Herpes simplex – EBV –VRS – Influenza viruses – Cytomegalovirus
TONSILLITIS	Adenovirus – EBV – Parainfluenza viruses – Other viruses (42%)
ACUTE OTITIS MEDIA (miringite bullosa)	Parainfluenza and influenza viruses
LARYNGOTRACHEITIS	Parainfluenza virus type 1 and 2 – Influenza viruses
RHINOSINUSITIS (predisposing to bacterial infection)	Parainfluenza and influenza viruses, – Adenovirus – Rhinovirus
LABYRINTH DISEASE	Herpes simplex – Varicella zoster – Rubella virus – Citomegalovirus
DEAFNESS	Parotitis (mumps) virus – Measles virus – VRS – Cytomegalovirus – Rubella virus – Herpes zoster – Parainfluenza and influenza viruses
LARYNGEAL PAPILLOMATOSIS	Papovavirus
FACIAL PARALYSIS	Herpes zoster

Table 2
The viral etiology of childhood deafness

Prenatal or congenital	Post-natal or acquired
Rubella virus	Measles virus
Citomegalovirus	Mumps (parotitis)
Herpes varicella zoster	Varicella zoster virus
HIV	HIV

2.1. Prenatal deafness

In prenatal deafness, a pathogen introduced during pregnancy can provoke an arrest or alteration of the normal development of the ear, even causing lesions on the already-formed hearing mechanism [6]. The most serious lesions manifest themselves in the first three months of pregnancy, especially between the seventh and tenth week, when the cochlea is developing; this would be considered a case of embriopathy. Fetopathy refers instead to lesions that form between the fourth month of pregnancy and birth. Since the hearing organ has already formed in these cases, patients do not generally suffer serious alterations although the inner ear is certainly sensitive. The viruses that most frequently cause prenatal deafness are rubella and citomegalovirus (CMV).

2.1.1. Rubella

Rubella is caused by an RNA virus of the Togaviradae family of the Rubivirus genus. Congenital rubella is typically passed on to the fetus from a primary infection in the mother. The virus invades the upper airways of the mother causing viremia and spreading into different sites including the placenta. It has been hypothesized that in the first gestational phases, the rubella virus provokes a chronic intrauterine infection. Fetal infection in the first trimester, particularly in the first 8–10 weeks, has an extremely high risk of malformations such as hypoacusia, cardiac and ocular defects (Gregg Triad); however, if the rubellum infection is contracted in the second or third trimester, it results in hypoacusia and pigmented retinas. Thus, the more precocious the maternal rubellum, the greater the risk of fetal infections and the more serious the fetal malformations (100% in the first month, 80% in the first trimester, 70% in the second trimester and 30% in the third). This reduction is likely due to either a maturation of the placenta after the first trimester which limits the transfer of the virus, or the greater resistance of the differentiated cells [5]. The deriving hypoacusia is generally sensorineural and bilateral and at birth can already be progressive or it can manifest itself later. The hearing damage seems to be caused by a “teratogenic” effect of interference with the normal development of the organ at the cochlear level [6,7]. Unlike other congenital infections, rubella is easily prevented. Between 12 and 15 months of age, a live-virus rubellum vaccine is administered along with a measles and mumps vaccination, giving the patient immunity to rubellum for about 15 years (MMR); a booster vaccination is administered before elementary or middle school. Women of child-bearing age who are not immune to rubella must undergo vaccination and not get pregnant in the following three months. Vaccination immediately after giving birth is advisable for mothers at risk of being infected.

2.1.2. Citomegalovirus

Citomegalovirus (CMV) is a DNA virus that belongs to the Herpesviridae family. It can go into latency and then reactivate and has been isolated in various sites including saliva, urine, breast milk, sperm, brain fluid, and amniotic fluid. *Congential CMV infection* is thought to be derived from transplacental infection from a primary or recurring maternal infection occurring in the first half of pregnancy. *Prenatal CMV infection* is contracted by contact with infected cervical secretions, breast milk, or blood derivatives. It is believed that maternal antibodies have a protective function and that most of these newborns are either born asymptomatic or are not infected by the virus in the case of contact. Many women who are infected by CMV during pregnancy are asymptomatic, but occasionally develop an illness similar to mononucleosis. It is still unclear if more serious lesions are a consequence of a precocious maternal infection or of a later one during the course of gestation. Nearly 10% of children with congenital CMV infection are symptomatic at birth. Manifestations include delayed intrauterine growth, premature birth, microcephalus, jaundice, petechia, hepatosplenomegalia, periventricular calcification, corioretinitis e pneumonia. The virus causes deafness by infecting the inner ear and altering the Organ of Corti. Moreover, it can cause malformations of the labyrinth of ethmoid and at the same time also lesions on the auditory tract due to secondary toxicity. The hypoacusia that establishes itself is sensorineural, almost always bilateral, and profound, generally regarding acute tones. Symptomatic newborns have a mortality rate of up to 30% and 70–90% of those who survive have neurological deficits such as hearing loss, mental retardations and visual disturbances [8–10]. A vaccine for CMV is still under research. Exposure to the disease in non-immunized pregnant women must be controlled, despite the fact that CMV is ubiquitous everywhere. Since it is frequent in children who attend preschools, pregnant women must observe all the common norms of good hygiene after contact with or being exposed to the urine or expectorate of such children [11,12].

2.2. Post-natal deafness

In post-natal deafness, numerous infective illnesses can be responsible for serious damage to the VIII nerve and the cochlear apparatus. A large part of hearing defects arising in childhood can be traced back to the intrauterine period. The most frequent forms are: viral meningoencephalitis (arbovirus, herpesvirus, mixovirus, poxvirus, etc.), mumps, chickenpox and measles.

2.2.1. Meningoencephalitis

Meningoencephalitis can be primitive or constitute the secondary complication of a viral infection. The forms of primitive meningoencephalitis can be both epidemic (arbovirus, poliovirus, echovirus, coxsackievirus illnesses), and sporadic (herpes simplex, varicella zoster, parotite) [13]. Secondary encephalitis, such as complications of a viral infection, probably have an immunological, pathgenic mechanism. Secondary encephalitis to rubella, mumps, measles, smallpox, cow's pox and other less defined illnesses are all examples. Currently, deafness caused by meningoencephalitis is not infrequent among the post-natal causes of deafness; in some cases it can be caused by a virus that, before birth, reach the cochlea via the external hearing conduct by way of the vascular system, causing a relatively symmetrical bilateral sensorineural hypoacusia which is either mild-serious or profound. In other cases, deafness is due to a meningoencephalital localization of liquor infection in the first four weeks of life as a complication of neaonatal sepsis (25%). Deafness caused by meningoencephalitis occurs more often in males and is found in 2/10,000 neonates born at full term and in 2/1,000 low-weight neonates. No vaccines exist for the described viral forms.

2.2.2. Mumps (parotitis)

Mumps (parotitis) is instead caused by a paramixovirus, spread through drops of infected saliva or through direct contact with material contaminated by infected saliva. The virus probably penetrates the body through the mouth. It can be found in saliva 1–6 days before the appearance of the swelling of the salivary glands and lasts throughout the duration of the illness (usually 5–9 days). An infection usually results in permanent immunity, even when there is unilateral swelling of the salivary glands. Although the illness can occur at any age, most cases occur in children between 5 and 10 years of age; it does not usually occur in children under 2 years old. Breast-fed children less than one year old are usually immune. The incubation period is 14–24 days. Deafness can be a complication in 5/10,000 cases of mumps. In 80% of cases, deafness is sudden and unilateral in the context of an acute infection in association with aseptic meningitis and often accompanied by tinnitus, ataxia, and vomiting. Hearing loss is profound and permanent for high frequencies and can go unrecognized. Damage is confined to the cochlear duct and consists in the degeneration of the vascular strip of the Corti organ, the degeneration of the upper membrane, usually more serious on the basal curve of the cochlea. Active immunization is obtained through a single-dose, live-virus inoculation between 12 and 15 months of age with a MMR vaccine. A booster dose is administered before starting elementary or middle school.

2.2.3. Measles

Measles, caused by a paramixovirus, is extremely contagious and is spread primarily through either the nasal and oral excretions of an individual in the prodrome or precocious eruptive stage of the disease or through the nuclei of drops dispersed in the air. The contagious stage of the illness extends from 2 to 4 days before the appearance of the eruptions until 2–5 days after their appearance. The virus disappears from the nose and pharynx secretions as soon as the eruption on the skin has cleared up. The incubation period is 7–14 days. Measles virus causes permenant, bilateral deafness in 1/1000 cases. Deafness appears suddenly at the same time as the cutaneous rash. The viral infection of the inner ear spreads through the vascular strip and destroys the structures of the cochlea as well as most of the nervous and ganglionic and fibers [14]. Measles infection can be avoided by administering a reduced, live-virus vaccine to children between the ages of 12 and 15 months (MMR). The vaccine confers long-term immunity and provokes an antibody response similar to that of natural measles. In some cases, the vaccine can provoke a light or asymptomatic infection that is not contagious. Sensitive subjects at risk of contracting measles can be protected if the live-vaccine is administered within 2 days of exposure. In other cases, such as pregnant women, or children under one year of age, an immunoglobuline specific measles vaccine (MIG) or a 0,25 ml/kg IM dose of serum immunoglobulin may be administered.

2.2.4. Chickenpox

Chickenpox is caused by the varicella-zoster virus (herpesvirus) and represents its acute, invasive phase, while the reactivation from its latent phase causes the herpes zoster illness. It is believed that chickenpox, which is extremely contagious, is transmitted through drops of saliva which are infected and even more infective during the brief prodromic period and the first phase of eruption. Incubation period is 14–16 days and transmission is considered possible 10–21 days after exposure. The deafness it causes can lead to the destruction of the nervous and sensorial cells of the neuroepithelia through a process of neurolabyrinthitis which can result in severe bilateral, sensorineural hypoacusia [15]. Chickenpox can be prevented by inoculating with a reduced, live-virus vaccine in all healthy children between 12 and 18 months of age, after which children who lack immunity to chickenpox may be vaccinated at any time. Subjects over 13 years old who have not been immunized must receive two doses of the vaccine, with a period of 4–8 weeks between doses. The severity of the disease can be lessened by administering an immunoglobuline anti-zoster (ZIG) or anti-varicella-zoster (VZIG) within 96 hours after exposure. Its use, however, is restricted to subjects at risk, like those affected by leukemia, immunodeficiency syndromes or other serious pathologies, and pregnant women. Neonates with mothers who were infected by chickenpox five days before giving birth or two days after are also candidates for such treatment [16,17].

3. Viruses that can cause inflammation of the respiratory tract

Viral respiratory infection is almost always a benign pathology. Its beginning is connected with the socialization of the child, and as such is most frequent during preschool. It noticeably interferes with the child's wellbeing and provokes significant medical-social costs.Unfavorable environmental factors (atmospheric pollution, passive smoking, etc.), precocious socialization, and predisposing immunological factors with immunological immaturity could all be predisposing factors. Viral respiratory infections are characterized by a series of acute episodes that can involve the entire respiratory system or a single sector (pharyngotonsillitis, otitis, rhinosinusitis, laryngitis, bronchitis, pneumonia) [18–21]. The damage that a viral infection can inflict on the mucous membranes of the upper respiratory tract are influenced by the reduction of the mucous flux and phagocytes as well as the increase in the bacteria's adhesiveness to mucus cells [22,23]. An upper-resipiratory viral infection is characterized by multiple processes. First, the virus replicates itself in the epithelium, spreading fragments of the disintegrated cells into respiratory secretions and demonstrating the presence of the virus, viral peptides, or viral nucleic acids [24,25].

The host then responds to the infection by producing a range of cellular products. Some, such as alpha-interferon, are specifically anti-viral. Others, such as interleukin, are aspecific. Specific antibodies are produced in sequence, for example IgM followed by IgG and IgA; the comparison of a high level of IgM without an increase in IgG is an index of recent infection (the comparison of blood examinations confirms the diagnosis but is only clinically useful for epidemiologic purposes.

Acute rhino, pharengeal and tonsillar inflammation, caused by viral infections [26] are some of the most common deseases found in pediatric populations. Less frequently, the pharangeal-tonsillar forms are accompanied by an involvement of the oral and or respiratory tract mucosa [27–29]. Such infections, in anglo-saxon countries, the term, Upper Respiratory Tract Infection (URTI) or "common cold" is used to describe an inflammation of the upper airways [30]. The episodes, which often reoccur, effect mostly preschool-age children and have socioeconomic repercussions, which are not related to the gravity of the pathology, but mostly to the increase in the requests for visits to the doctor, the costs incurred for treatment and the days of school and work lost by the children and the parents who must look after them. The etiology of the acute forms in the respiratory airways is, initially, of a viral nature in most patients, with later, secondary bacterial infections on the mucous lesions caused by the viral agents [31]. The transmission of the pathogens responsible for the URTI frequently occurs in public locations by direct or indirect contact with the nasal secretions or Plugge drops from infected subjects. Seasonability, which could increase or reduce sensitivity to such infections, constitutional factors, and an incomplete maturation of the immune system of the child are hypothesized to be pathogenic mechanisms. Multiple viruses are responsible for these infections as described in Table 1. The course of acute, unspecific viruses is quite variable but almost always concludes with a recovery within 2–5 days as long as other complications do not develop. The most common complications are infections such as otitis media (mostly in younger children), rhinosinusitis, satellite lymphoadenitis, spreading of the infection into the lower respiratory tract and obstructed respiration, and bronchial spasms in subjects with bronchial hyperactivity. Occasionally respiratory viruses are responsible for clinical pictures described as *the common cold* [32], caused by *picornavirus (rhinovirus, echovirus and coxackievirus)*, and *influenza syndrome* [8,33–35], caused by influenza viruses that initially strike the epithelium of the respiratory mucous membranes which other viral strains attach themselves to, aggravating and complicating the original clinical portrait [36,37].

Both herpangina and laryngotracheitis have a unique clinical picture. *Herpangina* is an extremely contagious illness caused by a *coxackievirus* characterized by a presence of a vesicular exanthema at the velopharyngeal mucous level and *acute or croup laryngotracheitis* [38–41] when viral infections are associated. The infections are caused by diverse viruses but more frequently by type 1 and type 2 parainfluenza viruses [42–44], which cause an inflammation of the tracheal and subglottic muscous membrane with a charateristic symptomology (inspiratory stridor and barking cough) occasionally relapsing with serious, obstructing respiratory complications [45–47].

4. Peculiar viruses

4.1. Herpes zoster oticus

The varicella-zoster virus (VZV) belongs to the herpesvirus group. It is a DNA virus that gives rise to chickenpox as a primary infection and to herpes zoster (HZ) as a localized relapse due to modifications of the pathogenic power of the virus and/or alterations of cellular immunity [38,48,49]. HZ is an acute cutaneous–nervous illness that is locally circumscribed and provoked by a resurgence of the VZV acquired during infancy and latent in one or more of the more sensitive ganglia of the dorsal roots of the spinal marrow and/or cranial nerves for a prolonged period of time (often decades); During the latency period the virus does not replicate itself or give any sign or symptom of its presence [50–52]. In particular, at the auricular level, the illness takes on the name *herpes zoster oticus* but it is also described in the auricular zone as *herpes zoster auris* or *Ramsay Hunt illness*, in honor of the author who, in 1907, described its characteristics and its correlation with the geniculate ganglion [53,54]. The illness is caused by a reactivation of the VZV in the geniculate ganglion of the facial nerve; through the sensitive nervous fiber, the virus reaches the skin and causes a characteristic centrifugal root vesicular eruption. We can clinically define four stages according to the involvement of the VII n.c. The diffusion of the virus from cell to cell must be impeded with the use of antiviral drugs (5 mg/kg acyclovir administered intravenously per day in three daily doses for 7–10 days followed by an oral administration for another 7 days); results of treatment with more recent antiviral drugs (such as famciclovir and valaciclovir) are promising, while a significant inflammatory reaction reactive in the nerve must be treated with cortisone-based anti-inflammatory medication (1 mg/kg/daily for ten days) and sometimes with surgical decompression [13]. Analgesics and local antiseptics should be added to treament with cortisones and antiviral medication.

4.2. Laryngeal papillomatosis

Laryngeal papillomatosis (LP) [55,56] is caused by subtypes of the human papilloma virus (HPV) which is a member of the Papova family of viruses [57]. Seventy subtypes have been described, but only HPV 11, HPV 6, and more rarely HPV 16 are specifically associated with laryngeal papillomas [58–60]. Typical of such a pathology is the multifocal nature of the lesion (>85% of cases), localized on the vocal cords in 60% of cases but also involving the upper-glottic plain (35%), the oropharynx, the bronchial tree and, rarely, the cervical esophagus. In the United States, the annual incidence rate of laryngeal papillomatosis is 4.3/100,000 in children and 1.8/100,000 in adults, with a prevelance of 5.7/100,000 [61,62]. This data is substantially analogous to that revealed in a 1991 Danish study [63] which registered an annual incidence in children of 3.6/100,000. Histologically, papilloma cosists of a cartilaginous fiber scaffolding with the presence of connective vascular tissue its surface surrounded by squamous epithelium. Keratinizing aspects are not observed on its surface. The course of this pathology is characterized by frequent relapses and aggravations that require frequent and repeated laryngoscopy and bronchoscopy to ablate the rapidly forming pappillose formations and to avoid obstruction of the airways [64]. Even if the illness is usually resolved by a spontaneous recovery, some cases can move toward an unfavorable prognosis at any time for no recognizable reason and involve the trachea, the bronchi and the lungs [65]. It is believed that HPV 11 has a greater propensity for a distal, pulmonary diffusion and that, moreover, therapeutic action, such as tracheotomy or repeated endolaryngeal ablation can favor the distal insemination of papillomas. The tracheal, bronchial, and pulmonary involvement occurs, according to various authors, in 2–4% of cases. Malignant degeneration of the laryngeal papillomatosis, is a rare, but serious event and leads to an unfavorable prognosis. Most described cases involve adults who have other risk factors, such as the use of tobacco, long-term illnesses, and previous exposure to radiation due to radiation therapy for papillomatosis. There is a greater probability of malignant transformation with HPV 16 but also HPV 6 and 11 are capable of oncologically transforming the nature of a cell culture [66]. In surgical treatment of laryngeal papillomatisis, many techniques are used: asportation with tweezers via indirect laryngoscopy, electro-cauterization, cryosurgery, direct asportation in larynfissure, endoscopic asportation with microlaryngoscopy in suspension. Currently, most surgeons prefer endoscopic laser surgery for its high precision and the haemostatic control which the technique permits [10]. More recent techniques include argon laser photo sensitization and hematoporphyrin derivatives, known as photodynamic therapy [67,68], and the technique with scaples and RF (“coblation”) which seems to avoid the modest heat damage and the edema which results from the use of the laser [69,70]; The same advantage is shared by ablation with microdebrider which is also more rapid than excision by laser. That is why it is coming ever closer to replacing the CO_2 laser as the ablative method of choice for use on children [71]. Despite the radical nature of the treatment, relapse is the norm. This makes reiterated procedures necessary with the possibility, occasionally, of having to resort to a tracheotomy. Such a procedure should be avoided for as long as is possible because of the recognized possibility of colonization on the part of the papillomas in the region of the tracheostomy and tracheobronchial tree. The risk of the tracheobronchial tree being colonized is also believed to be a consequence of the repeated intubations. The need to lengthen the amount of time between surgical asporation of the papillomas and the possibility of complete medical resolution have spurred many researchers to find adjuvant or resolving treatments. Recent studies have supplied a way to identify adjuvant therapies to control papillomatosis and its relapses such as interferon-alpha [56], acyclovir [72], indolo-3-carbinolo [73], retinic acid [74], metotressato, cidofovir [75–78]. Even if the above therapies have sometimes significantly reduced relapses of papillomas, we believe the most effective to be intralesional injection of cidofovir associated with surgical treatment [76]. However, none of them are able to eradicate the HPV genome from the mucous cells of the respiratory tract [79]. The most promising therapies for PL are based on both therapeutic and prophylactic HPV vaccines that are currently in experiemental phases [56,80,81].

4.3. Infective mononucleosis

The Epstein-Barr virus (EBV) or human herpesvirus 4 is a ubiquitous gammaherpesvirus that infects more than 95% of the world's population. The most common manifestation of the primary infection of this organism is infective mononucleosis (IM), a sometimes acute, but often asymptomatic clinical syndrome which more often strikes children, adolescents, and young adults [82]. It is a self-limiting lymphoproliferative illness connected to a first contact with the Epstein-Barr virus. The virus generally comes into contact with the mucous membranes of the oropharanx where it causes a localized primary infection from which it can circulate through the bloodstream.The period of incubation is not known, and to be the source of infection, is often misunderstood, even if it is known that it is mainly spread orally. In particular, the cells which host cells are mainly the B-lymphocytes and the cells of the human nasalpharanx are where the virus replicates itself. The B-lymphocytes transformed by EBV are the target of a multiform immune response. The immune response (production of antibodies) documents a primary EBV infection. The cellular immune response, consisting in part of the induction of an activated, postive T-lymphocyte CD8, is mostly responsible for atypical lymphocytes which is the consequence of a primary EBV infection. The virus can be found in the oropharangeal secretions of 15–25% of healthy adults who test positive for EBV. The reactivation of EBV is generally asymptomatic, the opposite of that of the Herpes simplex and varicella-zoster virus. EBV is relatively labile. It has not been isolated from environmental sources and it is not very contagious. In the majority of cases, it is believed that the incubation period is 30–50 days. The virus can be spread by the transfusion of blood derivatives but is more frequently passed on by oropharangeal contact (kissing) between a non-infected subject and a healthy carrier that asymptomatically secretes the virus from the oropharynx. During early childhood, infection occurs more frequently in lower socioeconomic classes and in conditions of overcrowding [83]. EBV has also been associated with African Burkitt lymphoma and some B-cell neoplasias in immunodepressed patients (especially transplant recipients, HIV or ataxia-teleangectasia patients) and to nasalpharangeal carcinoma [29,84,85]. These associations are based on seriologic evidence of an increased EBV activity and on proof of nuclear antigens (Epstein-Barr nuclear antigens, EBNA) and of EBV DNA found in tumor biopsies. It has been postulated that EBV places a role in some B-cell lymphomas, polyclonally stimulating and transforming the B-lymphocytes, making them more susceptible to a successive chromosome transfer to an evolution toward an oligoclonal or monoclonal lymphoproliferation. The classic symptomology of MI includes fatigue, fever, inflammation, lyphoproliferation, however, patients can also present all or only some of these symptoms. EBV infection in children is usually asymptomatic or with a light symptomology. Usually patients present with an illness that has lasted several days to a week, followed by fever, inflammation, and adenopathy. Fatigue is usually highest in the first 2–3 weeks. Fever reaches its peak in the afternoon or early evening with a temperature of around 39.5°C, but can even reach 40.5°.When fatigue and fever are the dominant signs (the so-called typhoid form), the beginning and the resolution can take longer. Inflammation can be serious, painful and sedating and can resemble streptococcica inflammation. Lymphoadenopathy can involve almost any group of lymphnodes but is usually asymmetrical; anterior and posterior cervical adenopathy is often relevant. The enlargement of only one lymphnode or a group of lymphnodes can be the only manifestation; in these cases, studies of the heterophiles can forgo lymph nodal biopsy or help the interpretation of alarming histopathological aspects. Splenomegaly, present in around 50% of cases, is at its maximum during the second and third weeks, manifesting itself through pain the upper left quadrant. Slight hepatomegaly can also be present as well as a pain on the hepatic percussion. Less frequent signs are malcularpapular eruptions, jaundice, periorbital edema, and palatal exanthema [40]. Infective mononucleosis is usually self-limiting. The duration of the illness is variable, usually about 2 weeks, but generally 20% of patients can go back to school or work after a week, and 50% after two weeks. Patients can usually begin their normal activites again after this period but sometimes the complete resolution of asthenia requires several weeks. Only in 1–2% of patients does asthenia last months. The decline happens in less than 1% of all cases and is generally caused by complications of the primary EBV infection (encephalitis, rupture of the spleen, airway obstruction). Generally, the diagnosis is clinical but it must always be confirmed by laboratory testing, and, in particular, identification of EBV. It should be mentioned that the tendency of a late positive score and the elevated possibility of false negatives. Treatment of MI is generally supportive and consists of antipyretic and/or analgesic drugs. The use of antibiotics is controversial while therapy is underway with cortisones, which is considered by some to be routine, but considered by other AA to be exclusively reserved for the most serious cases or complications. MI is generally considered to be a benign and self-limiting illness. However, in some, rare cases, complications can arise putting the life of the young patient at risk.

Serious hepatic complications are those which progress toward cirrhotic forms, Reye's syndrome or in extreme cases, toward Duncan's syndrome, a syndrome characterized by massive hepatitis linked to the X chromosome and caused by a defect in the immune response to EBV.

Respiratory complications are, in general, obstructive and linked to adenotonsillar hypertrophy or to serious interstitial pneumonia. Hematologic complications are particularly alarming and can lead to the bursting of the spleen as well as neurological complcations where encephalitis is the leading cause of death. In this regard, particular attention should be paid to Guillain-Barré's syndrome which is an inflammatory, demyelinating form that can complicate infective mononucleosis and cause a progressive paralysis of the respiratory muscles or rather a more or less diffused involvement of the cranial nerves.

Conflict of interest

None declared.

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