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Review Article

Frequently Ill Children from the Perspective of a Paediatrician/Clinical Immunologist

Jaromir Bystron*

Department of Allergy and Clinical Immunology University Hospital Ostrava, Czech Republic

***Corresponding Author:** Jaromir Bystron, Department of Allergy and Clinical Immunology University Hospital Ostrava, Czech Republic.

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Abstract

The author discusses the term "frequently ill children" in relation to the gradually maturing immune system. He underscores the specifics of different age periods and tries to prove that the cause of recurrent sickness episodes (especially the most common ones – respiratory tract infections) need not always lie in the immune system. Primarily, it is necessary to distinguish between primary (congenital) immune disorders, which often require lifelong specialized care, from secondary (acquired) disorders, for which it is most important to identify the underlying cause and try to eliminate it. An irreplaceable role in the diagnosis and care of frequently ill children is played by general practitioners caring for children and adolescents. The latter practitioners typically know the environment in which the child develops and have the capacity to perform basic immunological examination in order to identify severe immune disorders.

Keywords: *Frequently Ill Child; Immune Disorder; Congenital Immunodeficiency; Acquired Immunodeficiency*

Introduction

The present era, which we like to call "modern times", is characterized by some typical features. Our life tends to be hurried and every hour and minute are busy with a wide range of activities, especially occupational, social and family-related duties. We pay less attention to relaxation, rest, sleep and proper nutrition and every disruptive event that interferes with our life pattern can become upsetting. The interfering event that affects our daily routine may come in the form of child's illness. With our offspring fallen ill, we are forced to interrupt the established course of our lives. Since we are temporarily unable to place the child in a kindergarten or at school, the only choice is to stay home (unless we have a grandmother or can afford a nanny or an au-pair). Consequently, we need to take some days off work, cancel appointments, social gatherings etc. If that happens once or twice a year, it is still acceptable and manageable as a random occurrence. Yet, repeated events of this kind several times a year pose a more serious problem and the typical reaction of the parents coming for consultation is: "Doctor, the child is ill much too often, s/he certainly has an immune disorder". In a worse case, the parent might say: "The child has no immunity." Is it really a matter of immunity or is the problem elsewhere? Parents seek a simple answer and also a simple solution: "Doctor, give him/her something to support his/her immunity so that s/he is not ill so frequently".

In most cases, the problem is much more complex than a disorder of immunity and it usually involves the family, its lifestyle and habits, which is a fact the parents are reluctant to hear of as it would require that they change this style and habits. The situation with a frequently ill child is age-dependent, therefore, we will try to focus on the specifics of different age groups [1-5].

Immunity in infancy and preschool age

Gradually maturing immune system. The dynamics of the immune system's maturation can different significantly for each child. A very good indicator is the anamnestic inquiry into morbidity of the respective infant or toddler by asking parents or siblings. Information on how well the infant tolerated vaccinations and information on morbidity after the child's inclusion in a larger group – nursery, kindergarten or entry into primary school - is important.

Congenital immunodeficiencies. Serious immunodeficiencies become manifest soon after birth, in infancy, at the latest in toddler age, incurring serious infections of the respiratory tract, skin or severe diarrhoea and must be addressed as soon as possible by referral for examination in a specialized centre, mostly found in the paediatric ward of a regional or university hospital. Milder forms of immunodeficiency appear mainly after the inclusion of children in larger groups during toddler and preschool age. Initially, their treatment is symptomatic, based on the current condition, and is conducted by the general paediatrician. In case of recurrent or disproportionately long and severe ongoing infections, examination is necessary in a specialized allergology and immunology clinic, mostly located in every major city (currently there are approximately 3.5 medical positions in the field of allergology and clinical immunology per 100,000 inhabitants).

The warning signs of congenital immune disorders are as follows:

- 4 or more bacterial infections requiring antibiotic treatment within 1 year (otitis, bronchitis, sinusitis, gastrointestinal tract infections).
- Two or more serious bacterial infections (pneumonia, meningitis).
- Repeated infections or infections requiring a prolonged or intravenously administered antibiotic treatment.
- Recurrent infections located in different parts of the body.
- Insufficient increase in the level of protective antibodies after vaccination.
- A poorly thriving child with no apparent reason.
- Family history of immunodeficiency or recurrent infections.
- Extensive persistent candidiasis after 2 years of age.

Peer group entry The inclusion of a child in the peer group results in a significant expansion of contact with air-borne (droplet) infection, and in children who are not yet fully immunologically mature, this contact can cause more frequent catarrhal manifestations, especially in the upper respiratory tract. Evidence shows that this "physiological prominence - physiological immunization" is useful if the individual infections are mild and children are provided with an appropriate recovery period. The majority of such cases (up to 90 per cent) are viral diseases that do not require antibiotic treatment. Examination and treatment are fully within the competence of general paediatricians. In recurrent, severe or protracted cases, or severe or prolonged, examination in an outpatient allergy and immunology clinic is indicated. For this purpose, a recurrent case is defined as having more than 6-8 clearly diagnosed infections per year, requiring rest, antibiotic treatment or hospitalization, and a severe case is defined as requiring repeated administration of antibiotics or hospitalization.

Insufficient body hardening Inadequate clothing and insufficient physical activity are often the cause of increased catarrhal morbidity of the upper respiratory tract in children. For children performing physical activities, the clothing (number of layers of clothing) should be

the same as for adults performing similar activities. Excessive clothing causes increased sweating, increased fatigue and, consequently, a more intense exposure to the effects of cold gusts in a windy weather once the physical activity is stopped. The general principles applied in the past are still valid for infants who do not move on their own and are passively carried or transported in prams or special carts - the child´s body should be kept warm, and, for children moving on their own, the feet, head and neck must be dry and warm.

Incorrect diet composition This point primarily concerns excessive consumption of delicacies, sweets, sugary beverages, all of which are produced by the food industry primarily to induce children's addiction to sweet tastes and colours and do not respect the nutritional needs. The high content of sugar or other sweeteners, preservatives and many other artificial additives makes children addicted to these "foods" and children tend to consume smaller amounts of natural nutrients, vitamins, water, minerals from natural foodstuffs - fruits, vegetables and the like. This creates "latent alimentary deficiency-based secondary immunodeficiencies" that are difficult to quickly identify in the laboratory. The latter weakening of immune functions can be suspected when obesity, irritability, fatigue and recurrent illness are present in children.

Recurrent infections, especially of the upper respiratory tract, are a typical manifestation of the above causes. The crucial question is - What is a frequent illness? In this case, ´frequent´ is a consensual (agreed) term. In various clinical studies, increased morbidity in this age group of children is defined as the need for antibiotic treatment more than 6 - 10 times per year. Unfortunately, antibiotics are often overprescribed in some countries, considering the fact that up to 90 per cent of respiratory tract infections in children in this age group are caused by viruses. The administration of antibiotics in this case is not only ineffective, but also causes an imbalance of the natural intestinal bacterial population (intestinal microbiota), which may have a further adverse effect on the child's health and development.

The convalescence period should be strictly observed and the child should re-enter his/her peer group after achieving complete recovery, A child that has not yet fully recovered is always more prone to another illness. In collective facilities, parents should monitor the illness of other children or inquire about it with the teaching staff. On the one hand, the parents find out what kind of disease is currently on the upsurge among the children, and, on the other hand, this inquiry can help parents establish whether their child´s frequency of illness somehow exceeds the peer group average. Preparations designed for activating the immune system and/or supporting the maturation of immune functions, whether prescription drugs or over-the-counter formulas, should be consulted with a paediatrician who is familiar with the respective child and who can assess whether the condition warrants immunological intervention**.** Parents usually react emotionally and very subjectively. It is understandable that they wish to protect their child from various ailments and want to be able to go to work without taking a time off to care for the child at home, including a possible prolonged convalescence period, yet the fact of the matter may be somewhat different. Moderate morbidity in children may be completely physiological, representing a natural "training of the immune system".

A common misconception is that such a common illness can be cured when we send the child to a spa. Spa treatment is very effective for specific diseases (conditions after severe pneumonia, asthma, chronic respiratory diseases in paediatric populations), but not in common diseases. In this case, the spa can act as a transition to another kindergarten where the child meets other "frequently ill children", and, concomitantly, other types of mostly viral infections, resulting in the child falling ill again and the parents complaining about having the child ailing half of the time spent in the spa resort. It appears much better to use climate therapy (mountains, seaside) as part of an extended family vacation.

Immunity in school age and adolescence

Completion of the basic maturation of the immune system. The "maturation of the immune system and its functions" continues. Generally, non-specific immunity is fully mature but adaptive (acquired) immunity is still maturing in interaction with the environment. The levels of some antibodies (e.g., immunoglobulins) reach adult ranges no sooner than 6 - 10 years of age. This adaptive immunity creates an "immunological memory" and, therefore, the individual responds to an infection he or she had encountered in pre-school age

in a significantly faster and more effective manner. In consequence, the incidence of "common colds and infections" normally declines in preschool age. In non-technical terms, it is well characterized by the claim that„ Schoolchildren have already grown out of those common infections". In addition, the state-governed health care system itself helps to develop children's "immunological memory" through vaccination against serious diseases that caused widespread epidemics, high morbidity and mortality in the past. Nowadays, the former diseases are only sporadically seen thanks to compulsory vaccination (diphtheria, whooping cough, measles, rubella, mumps, polio, tuberculosis), although, unfortunately, certain "anti-vaccination activities" seem to contribute to decrements in collective immunity and to increased prevalence of paediatric infectious diseases, such as the recent bouts of measles, often with a serious course.

Examination of patients with suspected immune disorders

As with many medical disciplines, a very careful medical history is highly important. In the family history, we look for deaths in the family in infancy or toddler age, we ask questions about birth defects, chronic diseases, serious infections, frequent illnesses, especially in the patient's parents and siblings. In the personal history, we start from pregnancy (data on smoking during pregnancy, alcohol and drug consumption are relevant), maternal illness during pregnancy, we ask about the course of childbirth, foetal vitality after childbirth, thriving in the first days and months, postpartum jaundice and congenital malformations. We carefully determine the frequency and severity of infections in infancy and subsequent toddler age, as well as reactions to vaccination. Important information further includes the child's morbidity after joining the peer group (nursery, kindergarten and then primary school), and the course of common infections of childhood. In late school age and adolescence, questions about the frequency, course and severity of infections are supplemented with information about the family setting, mental resilience in crisis situations, and the environment in which the patient lives.

What is the basic and what is the specialized laboratory immunological examination

Laboratory examination of a patient with a suspected immune disorder begins with a routine examination of the blood count and differential count, which is supplemented with an examination of inflammatory markers (CRP, erythrocyte sedimentation rate) and examination of basic classes of immunoglobulins (IgM, IgA, IgG, IgE). This basic examination can provide us with important information about the current state of the body - leukocytosis or leukocytopenia, with specifications - lymphocytopenia, monocytosis, eosinophilia, anaemia, hypo- or agammaglobulinemia or elevated values of individual classes of immunoglobulins that contribute to the diagnosis of acute or chronic inflammation, allergies or immunodeficiency and may also be significantly indicative of a specific diagnosis - monocytosis in infectious mononucleosis, atypical forms of blood elements in haemoblastosis, increased eosinophils and total IgE in allergies or parasitic diseases. All these examinations are also available to general practitioners, have a very good informative value and are not economically demanding.

Basic immunological examination in patients with suspected immune disorders

- A detailed family and personal history with a focus on immune disorders.
- laboratory examination: sedimentation rate, CRP, complete blood count with differential, IgM, IgA, IgG, IgE.

In specialized immunological laboratory examination we specify the possible disorder by a more detailed scrutiny of individual components, including the examination of immunoglobulin subclasses IgG (IgG1 - 4), IgA (IgA1 - 2), examination of specific IgE for individual allergens, examination of complement components (C3, C4, total complement, C1 -INH, functional C1-INH), examination of phagocytosis, intracellular killing, examination of surface markers on lymphocytes and identification of subpopulations of lymphocytes (CD3 +, CD4 +, CD16 + 56 +, CD19 +, CD20 + and others), examination of general and specific signs of autoimmunity (ANA, ANCA, ENA, rheumatic factors, specific factors for organ autoimmunity), examination of functional activity of lymphocytes using lymph transformation tests, examination of basophil activation, skin tests with inhaled or bacterial allergens and numerous others, which are reserved for specialized clinics of

allergology and clinical immunology, rheumatology or some other specializations. Indication of the latter examinations and subsequent interpretation should be referred by the general practitioner (paediatrician) to an experienced specialist and the paediatrician should not induce large panels of these tests himself/herself.

Definition of recurrent respiratory infections

- In children 2 - 8 years of age: at least 3 infections in the last 3 months or 4 infections in 6 months or 6 infections per year.
- In children 8 years old and older: at least 2 infections in the last 3 months or 3 infections in the last 6 months or 4 infections per year.

An infection is considered to be a condition requiring at least a 3-day rest period, missed lessons at school or using antibiotics and meeting at least 3 of the following objective criteria: more than 3 days of subfebrile illness or a temperature rise above 38 centigrade for at least one day, acute rhinitis, sudden cough, sore throat, headache, otalgia, exacerbation of fatigue, with the possibility of arriving at a diagnosis of rhinopharyngitis, pharyngitis, laryngitis, tracheitis, bronchitis, pneumonia, sinusitis, otitis, tonsillitis and the like.

Principles of treatment of recurrent infections

- Thorough examination and treatment of the underlying cause of the current illness – substitution of body fluids, proteins, minerals, vitamins, targeted use of antibiotics, antivirals, antifungals according to the current patient status and sensitivity.
- Careful search for foci of infection (paranasal sinuses, middle ear, odontogenic infections, urinary tract, small subcutaneous abscesses, often adenoid vegetation in children, etc.) and proper treatment of the latter.
- Adequate convalescence, regimen measures and dietary measures after the steps referred to in points 1 and 2 above.
- Use of immunostimulatory or immunomodulatory agents if insufficient success was achieved with the previous three points.

Subsequent treatment approaches must then be focused on the identified primary cause, proper convalescence, and - in case of insufficient effect of these basic procedures - the right treatment includes a properly timed and carefully selected immunomodulatory therapy as a part of complex case management.

In cases where a specific immune disorder is identified as the cause of recurrent infections, immune substitution therapy is appropriate. If the immune response is manifested by escalated defensive inflammation, we use anti-inflammatory therapy and, conversely, if there is a need to activate some transiently weakened immune mechanisms, we use immunostimulatory agents. Immunostimulatory agents can be used only where the immune system is sufficiently formed in its individual components, that is, we can stimulate only something that is present in the body, but for certain reasons (exhaustion, starvation, chronic infection, extensive trauma, immunosuppressive therapy and the like) is temporarily insufficiently effective.

Should the frequently ill child with recurrent infections be treated by a general practitioner or a specialist?

If congenital immunodeficiency is suspected, as indicated by recurrent infections since birth (pneumonia, otitis, sinusitis, skin infections, more severe gastrointestinal tract infections, severe vaccination reactions), or if a more severe secondary immunodeficiency (e.g., conditions after major surgery, immunosuppressive or radiation therapy) is present followed by increased frequency and severity of infections, a more detailed immunological examination is clearly indicated and immunomodulatory treatment is then conducted according to the results of this examination and under the supervision of a specialist allergist/clinical immunologist. However, if the history-taking

process confirms a normal frequency and severity of infections in childhood and adolescence, and the increased morbidity turns out to be a completely new factor, there is no reason why the issue could not be addressed by a general practitioner. If necessary, even a general practitioner can perform a simple (and inexpensive) basic immunological examination (see above). However, even in these conditions, it is very useful to shed light on the beginning of the deterioration of the health condition with the subsequent development of recurrent respiratory infections. It can be a change of residence, a peer group entry, parents´ change of employment and of the workplace team, commuting via public transport, particular eating habits, depression based on difficulty solving personal problems, or underestimation of convalescence in the treatment of a moderate-to-severe infection. If such a cause can be unambiguously identified, it is necessary to address this cause first and then proceed to immunomodulatory treatment.

Conclusion

A frequently ill child - especially with recurrent upper respiratory tract infections – may not always be the result of an immune disorder. However, if an immune disorder is suspected, it is fully within the competence of a general paediatrician with a detailed history, analysis of the family environment and basic immunological examination to try to distinguish between primary-congenital and secondary-acquired immunodeficiency. If it is not a serious condition, it is also within his/her competence to try to treat these problems. In case of a more severe course or if a congenital immune disorder is suspected, a specialized examination in the outpatient clinic of allergology and clinical immunology is fully indicated.

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