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Transient hypogammaglobulinaemia of infants in children with mastocytosis – strengthened indications for vaccinations

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Abstract

Mastocytosis is a disease caused by the accumulation of mast cells (MC) in the skin and/or in other tissues. Both the cutaneous form of the disease (CM) predominating in children and the systemic form (SM) typical for adults are associated with the occurrence of MC mediator-related symptoms. The release of mediators can be induced by physical stimuli and/or specific triggering factors. The routine vaccination program performed in the majority of children in infancy can be considered as an additional factor provoking exacerbation of CM. Conscious of the important role of MC in the innate immunity, we have analysed retrospective data concerning the levels of immunoglobulins, an adaptive factor, in a group of 74 infants and toddlers with CM. The values corresponding to transient hypogammaglobulinaemia of infants (THI) were found in 8 (10.81%) of cases. Classification of the antibody deficiency was done according to the working definitions for clinical diagnosis of primary immunodeficiency of the European Society of Immunodeficiencies (ESID) Registry – version May 11, 2015. Following the retrospective data, the final diagnosis of THI cannot be made due to the young age of the study group. The percentage may significantly exceed the published incidence of THI, i.e. about 0.11%. The results of our study may indicate, importantly, a higher incidence of THI in childhood-onset mastocytosis than in the general paediatric population and strengthen indications for vaccinations. In conclusion, we suggest that THI may be considered as a new aspect of paediatric mastocytosis that requires further investigation.

Key words: *hypogammaglobulinaemia, mastocytosis, vaccination.*

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Introduction

Mastocytosis, a disease caused by accumulation of mast cells (MC) in one or more organs, affects both adults and children. It is a rare condition as far as the whole population is concerned, but among the patients of dermatological departments and clinics its frequency is higher [1]. MC accumulate particularly in skin, bone marrow, liver, spleen, and lymph nodes. The clinical manifestation of the disease is due to an unspecific degranulation of MC and the action of the mediators released. In some cases degranulation, apart from very intensive local or generalised redness of the skin, may result in dizziness, weakness, hypotension, or even loss of consciousness [2-5].

Two main categories of the disease have been described: cutaneous mastocytosis (CM) and systemic mastocytosis (SM). In the great majority of affected children the cutaneous form of the disease is diagnosed. CM is considered as a benign, transient disease limited to the skin, which is usually associated with MC mediator-related symptoms. The WHO distinguishes three major clinical manifestations of CM: maculopapular type (MPCM), diffuse cutaneous mastocytosis (DCM), and solitary mastocytoma of the skin. The most common forms are MPCM (47-75%) and mastocytoma (17-51%). DCM is the most severe, rare form of CM (1-5%) [6].

Childhood-onset mastocytosis rarely has a very severe course with the presence of frequent incidents of flushing

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or anaphylaxis, obturation of bronchi, chronic diarrhoea, osteoporosis resulting in pathological fractures, gastritis, or different forms of neurophysiological abnormalities [6, 7]. SM with bone marrow and internal organs involvement is a rare finding in children [8, 9]. Paediatric patients develop the first signs of the disease usually before the age of two years. Depending of the extent and activity of the skin lesions the course of the disease can affect more or less the everyday life of a child and his/her family [10, 11]. To objectivise the severity of cutaneous mastocytosis the SCORMA Index (SCORing MAstocytosis) was designed; a tool of semi-quantitative analysis of the extent and intensity of the disease with vast clinical applicability [4, 12].

The diagnosis of childhood-onset CM is made during a period of very intensive development of the child. This is also the time of numerous routine vaccinations against the most severe infective diseases of childhood. The coexistence of the first mastocytosis symptoms and the necessity of early vaccination reveals a dilemma that is sometimes hard to solve. The unspecific degranulation of mast cells is a hallmark of the disease, which means that any stimulus affecting a child, e.g. cold or warm temperature, pain, infection with or without fever, food, drugs, vaccinations, and many others, may cause massive release of mediators.

The crucial question arises as to whether the group of children with CM should be vaccinated, or in other words – should this group of children be temporarily deprived of the possibility of effective prophylaxis of serious, life threatening illnesses due to the mastocytosis in the skin? The problem of transient aggravation of clinical signs of mastocytosis after vaccination is of varying severity due to the heterogeneity of the disease confined in the SCORMA index [4, 12]. The clinical approach concerning the vaccination is different in children with a solitary mastocytoma than in those with DCM. The severity and frequency of MC mediator-related symptoms differ in patients with the same clinical form of mastocytosis limited to the skin. In all forms of CM, even a mechanical irritation of the lesional skin results in localised reddening and urticarial swelling of different intensity.

Conscious of the unclear pathogenesis of mastocytosis and having the opportunity to observe a considerably large group of infants and toddlers with this rare disease and recurrent infections, we have tried to discuss the problem of a clinical approach to prophylaxis in childhood-onset cutaneous mastocytosis.

Material and methods

Characteristics of the studied group

In our centre a group of 74 infants and toddlers with CM were simultaneously examined by a paediatric immunologist and dermatologist. There were 63 (85.13%) children with MPCM, nine (12.16%) with DCM, and two (2.7%) with mastocytoma. The age of the studied group ranged from four months to three years, the mean age was one year and eight months, and the median age was 22 months. There were 44 boys (59.45%) and 30 girls (40.54%).

All of them were vaccinated, the majority at a general practitioner's, some of them in outdoor clinics and some in hospital – according to the intensity of skin changes measured by SCORMA Index. All the children received antihistaminic drugs five days before the procedure. In all the cases in which the vaccination was done with preservation of good medical practice, no major complications were observed. Viable vaccines (rotavirus, mumps, measles, rubella, chicken pox) were given separately to avoid misdiagnosis of symptoms. There were children with observed transient and mild exacerbation of skin rash, but it could not be classified as a serious complication. In children with the most severe form of disease – DCM – the vaccinations were usually performed with retardation, but finally completed.

Methods

In a group of 74 young, vaccinated children with cutaneous mastocytosis, we analysed retrospectively the levels of immunoglobulins (IG) with the use of immunoturbidimetric method, immunochemical system Architect, Abbott. The blood samples were taken at the occasion of routine assessments after obtaining informed parental consent for clinical examination and blood analysis. The study was approved by the Medical Ethics Committee of the Medical University of Gdansk and was conducted according to the principles of the Declaration of Helsinki. The levels of all the classes of IG were interpreted according to the age of patients. In children with abnormal levels of IG, blood samples were taken twice in a three-month period. The data of patients with hypogammaglobulinaemia are presented in Table 1.

Results

In eight (10.81%) young children with different forms of CM we found insufficient levels of immunoglobulin G. There were five boys and three girls in the immunodeficiency group. According to the ESID Registry – working definitions for clinical diagnosis of primary immunodeficiency, version May 11, 2015, due to the young age of the studied group, what we found was unclassified antibody deficiency with a clinical picture of transient hypogammaglobulinaemia of infants. All the patients with hypogammaglobulinaemia had normal values of lymphocytosis, and no serious infections were noted in the group.

In our study group there were nine children with DCM. In these children almost the entire skin area was affected, and associated MC mediator-related symptoms were

Table 1. The characteristics of the group of children with coexisting cutaneous mastocytosis and hypogammaglobulinaemia

	Age and sex (year of life, M/F)	Form of cutaneous mastocytosis	Tryptase level	Hypogammaglobulinaemia	SCORMA Index
1.	1,M	MPCM	15.6	Low IgG, IgA, IgM	58
2.	1,M	DCM	134.0	Low IgG, IgA, IgM	84
3.	1,M	MPCM	3.02	Low IgG	37
4.	2,F	MPCM	38.0	Low IgG, IgA, IgM	59
5.	1,F	MPCM	3.0	Low IgG	32
6.	1,M	MPCM	5.3	Low IgG	40
7.	2,M	MPCM	3.8	Low IgG	35
8.	2,F	MPCM	3.64	Low IgG	35

MPCM – maculopapular cutaneous mastocytosis, DCM – diffuse cutaneous mastocytosis

present. Nevertheless, the routine vaccination program was performed in all of them, in seven cases with retardation. Only in one of the DCM children was hypogammaglobulinaemia found.

Discussion

The concentration of serum immunoglobulins alters with age to have practical implications for evaluation and clinical approach [13]. The outcome of hypogammaglobulinaemia in children, owing to the heterogeneity in the pattern of clinical presentations, is hard to predict, and in many instances the diagnosis can be made only retrospectively [14]. Also, transitions between original, fully diagnosed primary immunodeficiencies may occur over time [14]. The developmental age is the age of investment in adulthood, which is why the higher incidence of hypogammaglobulinaemia in our group of infants and toddlers with CM, who constitute a group subject to intensive prophylaxis programs, should be deeply analysed. THI frequency in published data ranges from 0.061 to 1.1 cases per a 1000 live births (0.11%) [15-17]. There are authors, and it is also our personal impression, who diagnose THI more frequently, but there is no precise and published epidemiological data, probably due to non-uniform criteria of the disease [18]. Among patients with primary immunodeficiency (PID) there is about 2% THI [19]. In our group with mastocytosis there were over 10% of THI patients. The male preponderance indicated in THI, approximately 2 : 1 [16], was also found in our study group.

The cause and pathophysiology of THI is unknown. Typically, all the laboratory studies, including the number of CD19+ B cells, are in normal or close to normal range. Children with THI may show symptoms of hypogammaglobulinaemia or may be asymptomatic. According to the data of Whelan *et al*., in a symptomatic group the clinical signs occur in 5% of infants under six months old, 50% present symptoms at the age of 6-12 months, and 25% become symptomatic at over 12 months of age [20]. The antibody titres to protein immunisations in THI are also in normal and near to normal concentrations, which means that this group of patients answers well to vaccinations [15-17]. The early childhood is the unique time when the decision concerning vaccinations has to be made at the presence of unspecific antibody deficiency and CM, even without a complete diagnosis.

Mastocytosis, especially the cutaneous form of the disease, is diagnosed mainly on the basis of the clinical picture and the result of histologic examination of skin samples. The disease is not widely recognised but the number of physicians diagnosing it has been growing. WHO classification was established in 2001 [21], and new standards were presented and introduced in 2007 [22]. The clinical approach to paediatric patients with mastocytosis has been discussed and it has changed in time [1-3, 23]. In available databases observations concerning the coexistence of hypogammaglobulinaemia and childhood-onset mastocytosis have not yet been reported. Moreover, in this group of children generally a higher incidence of serious infections was not reported and, similarly, was not observed in our study. However, the aspect of early hypogammaglobulinaemia may have significance with regard to increased susceptibility to autoimmune disorders in mastocytosis, also in adults [24, 25].

As for the aspect of vaccinations in mastocytosis, the literature data is also scarce. Brockow *et al*. presented a large study on risk factors of anaphylaxis in 120 patients with mastocytosis. Among them were 46 children with CM. In 10 of them anaphylactic reactions to different factors were reported; only one of them was linked to vaccination – in terms of time of occurrence [26]. Bankova *et al*. presented the description of a five-month-old boy with DCM, in whom the generalised bullous eruption was observed 24 hours after routine vaccination against seven pathogens – *Haemophilus influenzae*, protein conjugated pneumococcal vaccine, poliomyelitis, diphtheria, pertussis,

tetanus, and rotavirus [27]. The first signs of the disease appeared 12 hours after vaccination, starting with colicky pain and a day later continuing with blisters on the back, lower abdomen, and upper arms. The type of reaction is not very specific and may reflect the clinical picture of abortive course rotaviral infection after the vaccination with attenuated but viable virus. Moreover, the gastrointestinal tract is the source of complaints because of MC mediator-related symptoms in 19.5% of paediatric patients with mastocytosis [3]. Pucino *et al*. presented a short communication concerning the slightly higher incidence of adverse reactions at the first dose of mandatory vaccination in a group of 32 children with CM [28]. In our opinion, based on retrospective data obtained from 74 cases of infants and toddlers with mastocytosis, the reaction to vaccinations was good and the adverse effects mild. The possibility of coexisting hypogammaglobulinaemia in a child with mastocytosis should be taken into account while deciding about the vaccination program. Unquestionably, it is crucial to choose the right place of vaccination, sometimes different than in routine practice due to the affected skin, and to observe the child for a minimum of two hours after vaccination. In some cases, among them those with DCM, the vaccination should be preceded by several-days use of standard or enlarged dose of antihistamines (H_1-blockers) and ranitidine. There are also cases in which oral steroids are indispensable after the vaccination due to exacerbation of skin lesions. In those, the level of immunisation against the vaccines' antigens should be controlled 4-6 weeks after the last dose. Another task is to assess the levels of immunoglobulins, particularly in patients with coexisting recurrent infections, and to continue the immunological assessments if necessary.

In conclusion, the results of our study suggest that THI may be considered as a new aspect of mastocytosis. Observing the good tolerance of vaccinations in this group of patients we suggest the program should be as wide as possible with viable vaccines given separately. Mastocytosis, particularly the paediatric form of the condition, is still not a clearly understood disease. Therefore, further investigation on the subject is required, especially in the aspect of immunocompetence.

The authors declare no conflict of interest.

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