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Szczepienia ochronne u dzieci z mastocytozą

Prophylactic vaccination in children with mastocytosis

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Streszczenie

Szczepienia ochronne należą do podstawowych ogniw polityki zdrowotnej. W Polsce obowiązuje system powszechnych szczepień ochronnych, który jest systematycznie dostosowywany do zmieniającej się sytuacji epidemiologicznej chorób zakaźnych, a także aktualnej wiedzy medycznej, co ma swoje implikacje w prawodawstwie. Mastocytoza jest heterogenną chorobą, będącą w istocie rozrostem hematopoetycznym. Cechuje się zwykle łagodnym przebiegiem w grupie pacjentów pediatrycznych, u których zmiany są najczęściej ograniczone jedynie do skóry, a dolegliwości typowo ustępują przed okresem dojrzewania. Mimo to realizowanie programu szczepień ochronnych u dzieci z mastocytozą budzi wiele wątpliwości wśród lekarzy podstawowej opieki zdrowotnej, pediatrów, dermatologów i lekarzy innych specjalności, a także rodziców chorych dzieci. Szczepienia należą do egzogennych czynników mogących powodować aktywację mastocytów, co skutkuje uwolnieniem z nich substancji biologicznie aktywnych oraz nasileniem objawów mastocytozy oraz wiąże się ze zwiększonym ryzykiem anafilaksji. Jednak częstość niepożądanych odczynów poszczepiennych u dzieci z różnymi postaciami mastocytozy jest porównywalna lub nieznacznie większa od tej w populacji ogólnej, a najczęściej stwierdzane są łagodne miejscowe odczyny poszczepienne. Celem niniejszej pracy jest przedstawienie aktualnej wiedzy na temat bezpieczeństwa szczepień w tej grupie chorych dzieci oraz popularyzacja wiedzy związanej ze szczepieniami u chorych na mastocytozę. Autorzy pragną podkreślić, że mastocytoza u dzieci nie stanowi przeciwwskazania do realizowania programu szczepień ochronnych.

Słowa kluczowe: szczepienie, anafilaksja, mastocytoza, *mastocytoma*

Abstract

Prophylactic vaccination is one of the fundamental elements of health policy. Poland has a universal vaccination programme, which is systematically modified depending on the changing epidemiological situation of infectious diseases, as well as current medical knowledge, which has its implications in legislation. Mastocytosis is a haematopoietic neoplasm occurring in children, usually with a benign course, limited to the skin and resolving before adolescence. However, the implementation of the general prophylactic vaccination programme in children with mastocytosis raises many concerns among doctors and parents. Vaccinations are among the exogenous agents that may cause mast cell activation and release of biologically active substances, resulting in the exacerbation of mastocytosis symptoms and an increased risk of anaphylaxis. However, the incidence of adverse effects of vaccinations in children with different forms of mastocytosis is in fact comparable to or only slightly higher than in the general population, and vaccine-related events are usually mild and local. Unfortunately, there is a lack of understanding regarding vaccinations in children with mastocytosis both among general practitioners and parents. The aims of this paper are to outline the current state of knowledge on the safety of vaccinations in this group of patients, to promote knowledge related to vaccination in patients with mastocytosis, and to emphasise that mastocytosis is not a contraindication to vaccination.

Keywords: vaccination, anaphylaxis, mastocytosis, mastocytoma

INTRODUCTION

Mastocytosis is a clinically heterogeneous haematopoietic neoplasm characterised by excessive proliferation of monoclonal mast cells (MCs) infiltrating one or more organs, including the skin, bone marrow, spleen, liver, lymph nodes, and gastrointestinal tract[1–3]. Mastocytosis is a rare disease, with an incidence of 1/10,000 people[4]. In the paediatric population, it is slightly more prevalent among males, but after puberty, females predominate[5]. There are two peaks in the onset of the first symptoms of the disease – up to the age of three and after the age of 15. The emergence of the condition and/or exacerbation of symptoms during adolescence may indicate systemic mastocytosis (SM)[6,7].

The clinical picture of mastocytosis consists of symptoms resulting from the activation of MCs and the release of biologically active substances (including histamine, heparin, tryptase, chymase, prostaglandins, leukotrienes, cytokines and chemokines) under the influence of endogenous and environmental factors (Tabs. 1, 2) and associated with the accumulation of MCs in body organs, manifested by skin lesions typical of mastocytosis, as well as organomegaly and/or dysfunction of internal organs, most commonly the liver, spleen, gastrointestinal tract, and bones[8,9].

The most common form of mastocytosis among children is cutaneous mastocytosis (CM) (Tab. 3), accounting for approximately 90% of all cases of mastocytosis in patients under the age of 18. In this form, MCs accumulate in the skin, causing cutaneous changes and/or systemic symptoms as early as in the first year of life[11]. Maculopapular cutaneous mastocytosis (MPCM), also called utricaria pigmentosa, accounts for up to 90% of paediatric cases of CM. The lesions are macules or slightly raised papules in colours varying from yellowish to reddish brown. Two major morphologies of MPCM can be distinguished – monomorphic and polymorphic. The most common type of paediatric MPCM is polymorphic, in which lesions vary in shape and size. In children with polymorphic lesions, mastocytosis is usually limited to the skin. Monomorphic MPCM is more prevalent in adults, while in children monomorphic lesions are more often correlated with SM and persistence into adulthood, particularly when the lesions appear in late childhood or increase in number after puberty[11].

Mastocytoma is usually a solitary tumour from MCs in the skin, present on birth or appearing in first months of life. Mastocytoma lesions can be similar to MPCM but usually larger. Up to three lesions are regarded as mastocytoma, while more than three lesions are classified as MPCM. The skin lesions are typically present on the extremities. Mastocytomas can grow and change size, or involute, usually in preadolescence[11].

Diffuse cutaneous mastocytosis (DCM) does not present with distinctive lesions but the skin seems to be thickened, darker, and could be described as "orange peel". Typical is the involvement of the whole skin rather than small areas, and the risk of severe systemic symptoms due to mast cell degranulation is high[11].

The term "mastocytosis in skin" (MIS) refers to cases of patients with cutaneous manifestations of mastocytosis before the diagnostic process for SM is carried out[12].

Darier's sign is characteristic for all types of CM and appears as oedema, erythema or blisters after scrubbing lesions with high infiltration of MCs[11,12].

SM accounts for less than 10% of all paediatric mastocytosis cases. Children with SM almost always present with skin lesions with involvement of internal organs, including the bone marrow (Tab. 4)[11].

• Insect stings
• Drugs, opioids, aspirin, NSAIDs, antibiotics
• Muscle relaxants used in anaesthetic procedures
• Protective vaccinations
• Invasive procedures
• Sudden changes in ambient temperature, exposure to heat/cold
• Massage, friction, pressure of the skin
• Spicy food, alcohol
• Stress
• Physical effort
• Infections
• Fever
• Teething
• IgE-mediated allergies

Tab. 1. Possible mast cell activating factors[8]

Skin	Cardiovascular system	Digestive tract	Respiratory system
Itch Flushing Urticaria Angioedema Blisters	Hypotension Tachycardia Loss of consciousness	Abdominal pain Nausea Vomiting Diarrhoea Dyspepsia	Dyspnoea Wheezing
Other: headache, bone pain, anaphylaxis.			

Tab. 2. Symptoms caused by the release of biologically active substances due to activation of MCs[8]

Cutaneous mastocytosis (CM)	Maculopapular CM (urticaria pigmentosa): • monomorphic • polymorphic
	Diffuse cutaneous mastocytosis
	Cutaneous mastocytoma: • isolated • multilocalised
Systemic mastocytosis (SM)	Bone marrow mastocytosis
	Indolent SM
	Smouldering SM
	Aggressive SM
	SM with an associated haematologic neoplasm
	Mast cell leukaemia
Mast cell sarcoma	

Tab. 3. World Health Organization 5th Edition classification of mastocytosis[10]

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Major criterion • Multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s)
Minor criteria • ≥25% of all mast cells are atypical cells (type I or type II) on bone marrow smears or are spindle-shaped in mast cell infiltrates detected in sections of bone marrow or other extracutaneous organs • KIT-activating KIT point mutation(s) at codon 816 or in other critical regions of KIT in bone marrow or another extracutaneous organ • Mast cells in bone marrow, blood, or another extracutaneous organ express one or more of: CD2 and/or CD25 and/or CD30 • Baseline serum tryptase concentration >20 ng/mL (in the case of an unrelated myeloid neoplasm, an elevated tryptase does not count as an SM criterion). In the case of a known HαT, the tryptase level should be adjusted
If at least 1 major and 1 minor or 3 minor criteria are fulfilled → the diagnosis is SM.

Tab. 4. World Health Organization 5th Edition systemic mastocytosis criteria[10,13]

Paediatric mastocytosis usually has a benign course with a good prognosis, i.e. resolution by adolescence; this is in contrast to adults, where the systemic form may persist throughout life[7,14].

Diagnosis of mastocytosis in children is usually based on medical history and physical examination. Information about the occurrence of the symptoms associated with mast cell activation should be noted. Skin examination is usually helpful, as the skin lesions are characteristic[11]. Darier's sign is considered pathognomonic for CM[11,12]. Skin biopsy is not always needed and not recommended when skin lesions are typical. It is important to note that skin biopsy can trigger the degranulation of MCs. Punch biopsy in the diameter of 3 millimetres should be performed if the diagnosis of CM is uncertain. Staining for the receptor for the stem cell factor, also called CD117, is useful to detect MCs[11]. Abdominal ultrasound is also helpful for excluding organomegaly and lymphadenopathy[12]. Obligatory laboratory tests in children with CM include complete blood count, liver function tests, and serum tryptase level[11,12]. Tryptase is a protease produced in MCs, though a small amount is released by basophils and myeloid precursors. Normal levels range between 1 and 11.4 ng/mL[11], but experts recommend to consider levels >15 ng/mL as elevated[15]. Tryptase serum level is usually normal in children with CM and increased in SM. Serum tryptase levels above 20 ng/mL could be useful for identifying patients with SM. However, tryptase levels can be elevated in cases of extensive CM, such as DCM, as well as cases of MPCM, even without systemic involvement. Levels over 100 ng/mL may also be observed in the early stages of DCM and decrease over time[16]. Furthermore, tryptase can be elevated in patients with hereditary alpha-tryptasaemia (HαT) and after anaphylaxis in patients with or without mastocytosis[11,15]. While higher serum tryptase without organomegaly and systemic symptoms do not indicate SM, it should be strongly suspected in patients with baseline tryptase levels >20 ng/mL, liver or spleen enlargement, or abnormalities in the complete blood count[11]. *KIT* mutational analysis of peripheral blood should be performed in children suspected for SM, as it is a minor diagnostic criterion[10,11].

Bone marrow biopsy is done in cases of suspected SM. It is not routinely performed in children. It could be considered in patients with unexplained abnormalities in the peripheral blood such as cytopaenia or increased immature forms, unexplained abnormalities in liver function tests, hepatomegaly, splenomegaly, or persistent lymphadenopathy, severe systemic symptoms or *KIT* D816V mutation detected in peripheral blood[17].

ALLERGIC DISEASES IN MASTOCYTOSIS

IgE-dependent allergic diseases (atopic dermatitis, allergic rhinitis, asthma, food allergies or *Hymenoptera* allergy) may coexist in patients with mastocytosis, but the prevalence is comparable to the general population; they occur in 20–30% of people in western countries. IgE levels tend to be reduced in such patients, probably due to their binding to an increased number of MCs, with implications for the diagnosis of allergy in this group[9,14]. The incidence of anaphylactic reactions in patients with mastocytosis is approximately 30–50% in adults and 5.5–9% among children, which is significantly higher compared to the general population (0.02–0.5%) and the European population (0.3%)[9]. The release of mast cell mediators in patients with mastocytosis can be preceded by a variety of factors (Tab. 3), and a carefully collected history can be helpful in identifying them[11]. In children with mastocytosis, anaphylaxis is usually induced by drugs and foods[18]. Antibiotics, primarily beta-lactams and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common causes of drug-induced anaphylaxis in adults and children. Patients with mastocytosis and higher tryptase levels and widespread skin lesions are at an increased risk of anaphylaxis[18].

PROPHYLACTIC VACCINATION

Prophylactic vaccines, which are the main element of infectious disease prevention in the paediatric population, are among the exogenous inducers of MS activation, which may be related to the occurrence of vaccine adverse reactions (VARs) in children with mastocytosis[18]. Even though mastocytosis is not a contraindication to receiving vaccines included in the paediatric vaccination programme, the fear of VARs has a negative impact on the perception of vaccine safety among the parents of children with mastocytosis and physicians qualifying for immunisation in this patient group[19,20]. It is worth noting that protocols for reporting VARs vary from country to country, which may result in discrepant data across studies. What is more, there are no large and controlled studies in this group of patients[21,22]. Data from the literature mainly refer to children with CM, which is the most common type in this age group. Most studies have been conducted on small groups of patients, while severe VARs occur only as case reports[20,23,24]. Some studies have reported a higher incidence of adverse reactions in paediatric patients with all types of mastocytosis

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compared to the general population, but the reactions were mild, the patients did not require hospitalisation, and no adverse reactions occurred after subsequent vaccinations[20,24–26]. Other studies have shown that the risk is similar to that in the general population[3,19,27–29]. Adverse reaction to vaccine administration was observed in four cases of 634 vaccine doses given to patients with mastocytosis, which was greater than reported in the general population (2.3 cases per 10,000 doses per year). In that study, all reactions in patients with mastocytosis occurred after a hexavalent vaccine. The most common VAR was generalised urticaria. One child with severe DCM and a high serum tryptase level presented with a bullous reaction and bronchospasm[30]. Although there is no evidence that the reactions were due to MC activation induced by vaccine components, the experts claim that the procedure is a likely trigger of the reactions due to a close temporal relationship between the onset of clinical manifestations and vaccine administration[26]. A retrospective analysis of 102 patients with mastocytosis, including 67 adults – 63 with indolent systemic mastocytosis (ISM), two with MPCM, one with MIS, and one with aggressive systemic mastocytosis (ASM) – who received a total of 137 vaccine doses showed that 90% of vaccinated patients experienced no adverse reactions. No premedication was prescribed before vaccination in the study group. All adults tolerated the vaccines well and without adverse events. Seven children had mild adverse reactions and only in four cases the reaction involved clear symptoms of MC mediator release. Interestingly, in that group there were two patients with solitary mastocytoma, one with MIS and one with DCM. All four children had serum tryptase within the normal range[24]. Another retrospective study, conducted by the National Institutes of Health (NIH), analysed the safety of vaccination in 94 children with mastocytosis between 1984 and 2018. In 84 children (89.4%), there were no adverse reactions rated as severe or moderately severe according to the Centers for Disease Control and Prevention (CDC) classification. Only four children (4.3%) had unexpected reactions in the form of facial swelling, flushing, or exacerbation of skin lesions. Anaphylaxis occurred following the chickenpox vaccine in one child with MPCM at a tryptase level of 5 ng/mL. Anaphylaxis and other adverse reactions following vaccine administration were not found in any of the five children with a history of anaphylaxis, with a mean tryptase level of 115 ng/mL in this group[19]. In a Polish study of 74 infants and toddlers with CM, no major complications after vaccination were observed. There was only one patient with mild and persistent exacerbation of skin rash. All the children received antihistaminic drugs five days before the procedure[31]. Different issues are associated with the oral rotavirus vaccine. Gastrointestinal complaints because of MCs mediator-related symptoms occur in 19.5% of paediatric patients with mastocytosis[5]. Abdominal pain or diarrhoea after rotavirus vaccination may not be a symptom correlated with mastocytosis and MCs mediator release, but also abortive course of rotavirus infection after the vaccination with an attenuated but still live virus[31].

Most VARs are mild, localised, diffuse and transient; they usually involve the skin and may take the form of pruritus, paroxysmal erythema (flushing), urticaria or exacerbation of existing skin lesions – redness, appearance of blisters, or facial oedema. Mild bronchial obstruction, abdominal pain, vomiting, diarrhoea, fever and febrile convulsions are rarely observed[11,19,24,30,32]. Only one case of anaphylaxis has been definitively linked to vaccination in a child and occurred following chickenpox vaccination[19]. Isolated cases of cutaneous manifestations of mastocytosis following vaccination in children have been published, as well as mastocytoma arising at the site of hepatitis B vaccine administration[33–35]. VARs have been associated with monovalent and polyvalent, live and attenuated vaccines, intradermal, subcutaneous, intramuscular injections and oral rotavirus vaccine administration[18,24]. One study showed a much higher risk of adverse reaction after hexavalent vaccine[30]. Usually, VARs did not recur after a subsequent dose of the same vaccine[18,28]. Interestingly, according to the literature, COVID-19 infection does not increase mast cell activation symptoms in most patients[36].

RECOMMENDATIONS

There is a consensus among the experts that mastocytosis alone is not a contraindication to vaccines in patients with mastocytosis[16]. However, experts hold varied opinions regarding the simultaneous administration of multiple vaccinations and the use of premedication. Baseline levels of total tryptase combined with extensive skin involvement may be helpful in identifying patients at risk of severe VARs during the activation of MCs in paediatric mastocytosis[37]. Although the evidence is weak, children with DCM are at an increased risk of VARs, especially with the first administration of the vaccine[11,32]. Many authors have demonstrated the efficacy of premedication prior to vaccination, though a review of the literature does not allow for conclusions to be drawn on the usefulness of premedication regimens with oral antihistamines, systemic steroids or leukotriene receptor inhibitors[32]. Children with DCM may be particularly sensitive to a number of mast cell degranulating agents, including prophylactic vaccinations[8]. Patients with mastocytosis at a high risk of anaphylaxis should be premedicated with H1-antihistamines taken 30 to 60 minutes before vaccination[22]. Premedication with prednisone (up to 0.5–1 mg/kg) could be recommended but there is concern that corticosteroids may influence vaccination efficacy[8,22,32]. The benefits of H2-antihistamines and montelukast in premedication have not been well documented and the addition of these drugs can be considered on a case-by-case basis, once risk stratification is done[22]. The importance of post-vaccination fever as a trigger for MC degranulation is also highlighted, so additional premedication with paracetamol, with follow-up for possible

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febrile conditions, is indicated[8,32]. On the other hand, in some studies enrolling patients with mastocytosis vaccinated without premedication, the frequency of VARs was comparable across different studied groups[24]. Children with mastocytosis should not be given multiple vaccinations during the same visit, especially live vaccines (rotavirus, mumps, measles, rubella, chicken pox) to avoid misdiagnosis of symptoms and adverse reactions[32,38]. A Work Group Report of the Mast Cells Disorder Committee, American Academy of Allergy, Asthma and Immunology encourages to avoid hexavalent vaccine in patients with mastocytosis, based on one study where all adverse reactions occurred in patients vaccinated with a hexavalent vaccine[26]. Other studies did not confirm these findings[18,24]. What is more, some experts highlight that the procedure is a more probable factor in MC degranulation, which is why polyvalent vaccines should be preferred, as they contain fewer antigens and to minimise skin irritation with multiple injections[38]. Studies show that the risk of adverse reaction is greater after the administration of the first dose of the vaccine and usually do not occur after subsequent doses. Consequently, the administration of the first dose of the vaccine to children with mastocytosis should be done with enhanced surveillance and monitoring of the child's condition for 30–60 minutes following vaccination[11,22,24]. During this time, the patient and/or parent/guardian should be educated on how to recognise the symptoms and warning signs that require reporting to a medical centre, and the indications for an epinephrine autoinjector[25,27,29,39]. However, in a study involving 133 children with MPCM, 69% received an epinephrine autoinjector prescription, but it was used in only one patient after reaction to food. This suggests that routine prescription of epinephrine to all children with CM should not be recommended. Instead, it should be limited to groups with extensive skin involvement, high serum tryptase levels, and symptoms of severe MC degranulation[40]. In addition, in patients who have experienced VARs, a modified schedule may be helpful in identifying the antigen causing the reaction[18,26–28]. Importantly, in the event of an adverse vaccine reaction, the patient should be referred to an allergologist to rule out allergies to vaccine components (including gelatine, dextran, polymyxin or latex)[41]. Individuals with a known allergy to a vaccine ingredient should be vaccinated with a product not containing the allergenic substance, if possible. Potential cross-reactivity between polyethylene glycol and polysorbate must be considered[22]. With regard to messenger RNA (mRNA) vaccines against COVID-19 in adults, experts highlight that the only well-established contraindication to vaccination is a known or suspected allergy to an ingredient of the vaccine. The available studies do not report an increased risk of adverse reactions to vaccination in children under 16 years of age[22]. To the authors' best knowledge, there are no reported cases of serious adverse reactions after COVID-19 vaccination in children with mastocytosis.

CONCLUSIONS

Mastocytosis is not a contraindication to vaccination, either in children or in adults, however, extra caution is indicated. Each patient requires an individual approach. In some cases, premedication should be considered.

Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

Author contributions

Original concept of study: PB. Collection, recording and/or compilation of data: BP. Analysis and interpretation of data: BP, MP. Writing of manuscript: BP, MP. Critical review of manuscript: MP. Final approval of manuscript: MP.

Piśmiennictwo

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