Primary ciliary dyskinesia associated with multiple drug intolerance syndrome: a case report

Dyskinésie ciliaire primitive associée a un syndrome d'intolérance médicamenteuse multiple : à propos d'un cas clinique

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Abstract

Introduction: The term multiple drug intolerance syndrome is used for patients who express adverse drug reactions to three or more drugs without a known immunological mechanism. It is a distinct clinical entity, different from cross-reactivity. The symptoms can range from a benign rash to life threatening syndromes like drug reaction with eosinophilia and systemic symptoms.

Case report: We report the case of an 8-year-old child with primary ciliary dyskinesia complicated by bronchiectasis who presented multiple drug intolerance syndrome.Through this observation; we discuss the diagnostic elements of this syndrome.

Conclusion: In the absence of validated criteria for diagnosing multiple drug intolerance syndrome, a detailed history is essential, especially to identify the warning signs and the risk factors.

Key words: adverse drug reactions, antibiotics, hypersensitivity, bronchiectasis.

Résumé

Introduction : L'intolérance médicamenteuse multiple est caractérisée par des réactions vis à vis de 3 médicaments ou plus et en l'absence de tout support immunologique connu. Elle est différente des réactions médicamenteuses croisées. La symptomatologie clinique est très variable allant d'une éruption cutanée bénigne au syndrome d'hypersensibilité médicamenteuse systémique avec éosinophilie et des réactions médicamenteuses systémiques sévères.

Cas clinique : Nous rapportons l'observation d'un enfant atteint de dyskinésie ciliaire primitive compliquée de bronchectasie associée à une intolérance médicamenteuse multiple. A travers cette observation, nous discutons les éléments diagnostiques de ce syndrome.

Conclusion : En l'absence de critères validés pour diagnostiquer le syndrome d'intolérance médicamenteuse multiple, une anamnèse détaillée est indispensable pour identifier les signes d'alerte et les facteurs de risque.

Mots -clés : réactions indésirables aux médicaments, antibiotiques, hypersensibilité, bronchiectasie

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INTRODUCTION

Multiple-drug intolerance syndrome (MDIS) is described as a clinical entity characterized by adverse drug reactions to three or more drugs without a known immunological mechanism [1]. The prevalence of MDIS in the general population ranges between 2.1 and 6.4% [2,3].Despite its rarity, MDIS poses a diagnostic and treatment challenge [4].In children, the management of this syndrome is much more challenging [5]. Prescribing indispensable drugs may be life threatening and the use of alternative treatments may be less effective [6]. Herein, we present the case of an 8-year-old boy suffering from primary ciliary dyskinesia (PCD) and multiple drug intolerances.

CASE REPORT

We present according to the CARE guideline [7], the case of an 8-year-old boy known to have primary ciliary dyskinesia since the age of 3 years complicated by bronchiectasis. He also has a family history of MDIS with atopy and PCD in his older brother. The clinical events started since the age of 14 months with respiratory symptoms, urticaria and facial edema (Event 1, Table 1). These symptoms appeared within two hours of taking amoxicillin. Symptomatic treatment was remarkably successful as it gave a rapid regression in the edema and the respiratory symptoms. At the age of 2 years, he was admitted for gastrointestinal disorders (diarrhea and vomiting).They appeared within 24 hours of taking pristinamycin (Event 2, Table 1). These symptoms disappeared rapidly after the treatment was stopped. The drug was reintroduced one year later without incident. At the age of 3 years; he was prescribed ampicillin for purulent angina. Seven hours after the first intake, he developed a generalized rash that disappeared quickly after ampicillin withdrawal (Event 3, Table 1). Another incident occurred at the age of 4 years, during a hospitalization for recurrent airway infection, which was treated with intravenous rifampicin. Ten days after the first intake of rifampicin, the patient developed a fever of 40°C associated with leukopenia. He was switched to imipenem (Event 4, Table 1). Two days after the first dose of imipenem, the child presented a maculopapular exanthema on the lower limbs with rapid generalization of the rash (Event 5, Table 1). At the age of 5 years, an erythema with bronchospasm occurred one day after starting clarithromycin. The treatment was stopped and he had an injection of corticosteroid. All the symptoms disappeared within one hour (Event 6, Table 1). The last event occurred two days after starting azithromycin, the patient presented a generalized erythema with fever (40.5°C). Blood cell count revealed leukopenia (leucocytes: 2040 white blood cells /mm^3, normal range: 5000-10 000 white blood cells/mm^3) and a platelet count of 139 000 platelets/mm^3 (normal range: 150-450 10^3 platelets /mm^3) (Event 7, Table 1). Apart from penicillin, all other drugs were reintroduced to the same patient after receiving H1-antihistamine premedication. No adverse events were noted.

Table 1. Summary of the different adverse drug reaction with the involved drugs and their imputation score [8]

N°. of event	Type of event	Delay	Drug involved		Imputation score	Interpretation
			Molecule	Therapeutic class		
1	Urticaria Facial edema respiratory gene	2 hours	Amoxicillin	Pénicillin	I2	Possible
2	Digestive disorders	1 day	Pristinamycin	Synergistine	I2	Possible
3	Generalized rash	7 hours	Ampicillin	Pénicillin	I3	Plausible
4	Fever Leucopenia	10 days	Rifampicin	Antitubercular	I2	Possible
5	Maculopapular exanthema	2 days	Imipenem	Carbapenem	I2	Possible
6	Bronchospasm	2 days	Clarithromycin	Macrolide	I1	Doubtful
7	Fever Leucopenia Thrombocytopenia	2 days	Azithromycin	Macrolide	I2	Possible

DISCUSSION

Children, especially those with susceptible chronic diseases requiring a frequent use of drugs, are at a higher risk for MDIS. In the case under study, the patient presented seven different events, including skin manifestations, edema, fever, cytopenias, as well as respiratory and gastrointestinal disorders. These events were associated with different drug classes having no common structure: penicillin, carbapenem, antitubercular, synergistine , and macrolide. The major limitation of our case study is that each event was managed in a general paediatric department and some data were missing. PCDs are rare genetic diseases caused by congenital abnormalities in both the structure and the function of the motile cilia [9]. Symptoms which are quite varied they include respiratory, ear, nose and throat symptoms [10]. Antibiotic therapy is the cornerstone of treatment for recurrent airway infections in PCDs. Little data is currently available on MDIS. To the best of the authors' knowledge, the association of MDIS and DCP has never been reported before. The clinical manifestations are varied, ranging from a simple urticaria to fatal anaphylactic shock. The mechanism of MDIS is still unclear. The absence of validated criteria for diagnosing MDIS and the wide variation in the presentation of this syndrome represent real obstacles to understanding its etiopathology [11]. The most frequently accused drugs and biological substances are anti-infective and non-steroidal anti-inflammatory drugs [1,12]. The most common adverse reactions are mainly cutaneous [1]. These are often maculopapular exanthems, mislabeled rashes or urticaria. Severe anaphylactic reactions are rare in children. According to the study by Macy and Ho [2], severe adverse events were identified in 0.2% of children. The most frequently reported risk factors include females, advanced age and multiple co-morbidities [12]. Other studies reported genetic and psychological factors [2,13]. As described, our patient's older brother is also with MDIS. MDIS is a diagnosis of exclusion. Diagnosis is based mainly on a detailed analysis of the clinical history, skin tests (if available and validated), and drug provocation tests (if indicated).The efficiency of biological tests remains limited [14,15].A negative test result is useful for ruling out an allergic hypersensitivity reaction. Unfortunately, however, these tests target only specific drugs or drug classes. Drugs associated with serious adverse events should be avoided and replaced, if possible, by alternative treatments. When the drug involved is irreplaceable and has caused an anaphylactic reaction, desensitization protocols should be considered. Children reporting reactions more or less suggestive of drug hypersensitivity should undergo an allergological assessment. In cases of mild reactions such as maculopapular rash, gastrointestinal disorders or drug fever, the drug can be safely reintroduced [2,16].

CONCLUSION

Children, especially those with susceptible chronic diseases requiring more frequently the use of drugs, are at a high risk of MDIS. The absence of validated criteria for diagnosing MDIS and the wide variation in the presentation of this syndrome hinder our understanding of its etiopathology. Therefore, a detailed history is essential, especially to identify the warning signs and the risk factors.

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