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Short communication

Vaccination coverage of patients with inborn errors of metabolism and the attitudes of their parents towards vaccines

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ABSTRACT

To evaluate vaccination coverage of children and adolescents with inborn errors of metabolism (IEMs) and the attitudes of their parents towards vaccination, the vaccination status of 128 patients with IEM and 128 age- and gender-matched healthy controls was established by consulting the official vaccination chart. In children with IEMs, compared with healthy controls, low vaccination rates and/or delays in administration were observed for pneumococcal conjugate, meningococcus C, measles, mumps, rubella, diphtheria-tetanus-pertussis-inactivated polio, Bacillus Calmette–Guerin, and influenza vaccines. Among the parents of IEM patients, vaccine schedule compliance was primarily driven by the doctors at the hospital's reference centres; among the parents of the healthy controls, compliance was driven by the primary care paediatricians. These results show that IEM patients demonstrate sub-optimal vaccination coverage. Further studies of the different vaccines in each IEM disorder and educational programmes aimed at physicians and parents to increase immunization coverage in these patients are urgently needed.

1. Introduction

Communicable infectious diseases place patients with inborn errors of metabolism (IEMs) at high risk of metabolic decompensation, with potentially catastrophic consequences [1]. Moreover, some patients with IEMs also have an associated immunodeficiency [1]. Consequently, the prevention of infectious diseases in patients with IEMs can be clinically important, and vaccines could play a relevant role in their treatment. However, vaccines themselves can cause problems because they can deteriorate the metabolic equilibrium of affected patients, particularly when they cause the same, albeit less severe, metabolic changes that are usually associated with the disease they are meant to prevent [1]. Furthermore, vaccines could be less effective in patients with both IEMs and immune dysfunction [1]. Thus, some experts maintain that although no contraindication to routine vaccinations in any of the IEM databases could be found, special caution and close follow-up after vaccine administration should be considered in patients with IEMs associated with a tendency for rapid metabolic decompensation or with immunodeficiency [2,3]. More recently, Klein et al. have suggested that in patients with IEMs, vaccines should be administered, but the risk of metabolic decompensation should be primarily considered [4].

However, data regarding vaccination coverage of children and adolescents with IEMs are sparse, and no study has ever been performed to evaluate physician compliance to the few available recommendations. Moreover, the attitudes of parents of patients with IEM to vaccinations have never been evaluated. The main aim of this study was to obtain data on vaccination rates among children with IEM and attitudes towards vaccination among their parents.

2. Materials and methods

This study, which was performed between November 1, 2013 and March 30, 2014, and approved by the Ethics Committee of the Hôpital Necker-Enfants Malades (Paris, France), involved patients with IEM who were regularly followed up at the Hospital's Unit of

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Metabolism. All of the 132 patients with IEM who were regularly followed up at the Hospital's Unit of Metabolism were considered eligible for the study. Parents of 128 of them accepted to participate and signed a written informed consent in which they gave their approval for collecting information on their children's vaccination status and adverse events after vaccine administration. The diagnosis of each syndrome was based on clinical findings and laboratory testing, including tandem mass spectrometry, histologic findings and genetic testing showing alterations specific to each patient [5]. On the basis of age and sex of enrolled children, a group of age- and sex-matched healthy subjects who were admitted to the outpatient clinic of the same institution for health controls during the study period was enrolled as a control group.

The vaccination statuses of the patients and controls were determined by consulting the official vaccination chart, which was issued by the "Centres de Vaccinations" in the geographic areas in which the children lived. Data regarding diphtheria (D), tetanus (T), pertussis (P), polio (IPV), hepatitis B (HB), *Haemophilus influenzae* type b (Hib), pneumococcal conjugate (PCV), meningococcus C (MCV), measles, mumps and rubella (MMR), Bacillus Calmette–Guerin (BCG) and influenza vaccines were collected. All children and adolescents were considered to be fully vaccinated when they had received the doses of each vaccine at the suggested time, according to the recommendations of the French National Immunization Plan that were in use when they were born [6]. Moreover, the parents were administered a questionnaire (which was created and revised after pilot testing) soliciting information regarding their opinions of vaccination and questioning who primarily influenced their decisions regarding vaccination. Specific questions regarding the influenza vaccination, which is recommended by the National Immunization Plan for patients with IEM [6], were included. Regarding adverse events, parents were invited to mention those clinically relevant in their opinion, those for which drug administration was required, those that required children's hospitalization, and those for which a change in diet or lifestyle.

The enrolled patients were divided into three groups considering their theoretic risk of metabolic decompensation following vaccination. In particular, children with amino acid disorders, organic acidemias, urea cycle disorders, fatty acid oxidation disorders, mitochondrial disorders, glycogen storage diseases (GSD) types 0, I, III, VI and IX were considered sickest children because at higher risk of morbidity and/or mortality with catabolic event; children with lysosomal storage disorders, peroxisomal disorders, and purine and pyrimidine disorders were categorized as chronic because suffering from a slowly progressive condition; children with phenylketonuria, disorders of carbohydrate metabolism and GSD types II, IV, V, VII, and VIII were considered stable because not expected to deteriorate clinically even with illness. Before the analyses differentiated for disease's group, all the groups of IEM children were considered together and compared to the healthy controls. The significance of results did not change and in order to look at differences between diseases' categories the comparison was performed between each IEM category and healthy controls. A contingency table analysis using the chi-square test or the Fisher exact test, as appropriate, compared the between-group differences. The ordered categorical data were compared using a Cochran–Armitage trend test. All tests were two-tailed, and a p value of <0.05 was considered to be statistically significant. The data were analysed using SAS, version 9.2 software (SAS Institute, Cary, NC, USA).

3. Results

A total of 128 patients with IEM and 128 healthy controls were enrolled in the study. Table 1 summarizes the characteristics of the study population.

Table 2 shows the vaccination rates for the studied vaccines and the timeliness of administering each recommended dose. In the three groups of children with IEM, the vaccination rates and administration time for the hexavalent vaccine were similar to those found in the healthy subjects. On the contrary, the proportion of patients with IEM who received PCV was significantly lower than that of healthy children ($p < 0.05$), with the lowest values in the patients defined as chronic (23.3%) and with some significant delays for the primary series in the patients with IEM compared with the healthy controls ($p < 0.05$). MCV coverage was significantly lower only in the sickest patients compared with the other groups with IEM and the healthy controls ($p < 0.05$ for all comparisons), but significant delays in vaccine administration were observed in the three groups of patients with IEM compared with the healthy controls ($p < 0.05$ for all comparisons). MMR vaccine coverage was significantly lower in the three groups of patients with IEM than in the healthy controls ($p < 0.05$ for all comparisons), with significant delays in administration of the second dose in patients with IEM compared with healthy controls ($p < 0.05$ for all comparisons). When starting school, booster doses of DTP-IPV were given significantly less frequently in the patients than in the controls ($p < 0.05$ for all comparisons), with the lowest coverage found in chronic children (35.0%); note that there was no delay in administering the booster to the patients who had been vaccinated. BCG vaccination rates were similar in the three groups of patients with IEM and controls, although a significant delay in vaccine administration was observed in the sickest children compared with the

Table 1
Demographic and clinical characteristics of patients with inborn errors of metabolism (IEMs) and healthy controls.

Characteristic	Sickest patients with IEMs ($n = 82$)	Chronic patients with IEMs ($n = 30$)	Stable patients with IEMs ($n = 16$)	Healthy subjects ($n = 128$)
Age of the patient, median (range) years	7 (0.4–17)	7.75 (1–17)	8.5 (2.3–17)	7.79 (0–17)
Gender, males (%)	50 (60.9)	22 (73.3)	10 (62.5)	82 (64.1)
Ethnic origin, No. (%)				
Caucasian	38 (46.3)[1]	18 (60.0)	8 (50.0)	65 (50.8)
Other	44 (53.6)	12 (40.0)	8 (50.0)	63 (49.2)
Age of patients' parents, median (range) years	38 (20–64)	41.5 (29–56)	38 (25–56)	39 (20–65)
Gender of parent who filled in the questionnaire, women No. (%)	71 (74.4)	19 (63.3)	14 (87.5)	97 (75.8)
Number of siblings, median (range)	2 (1–7)	2 (1–6)	2 (1–4)	2 (1–6)
Diagnosis (No.)	Urea cycle disorders (26), mithocondrial disorders (15), organic acidemias (14), glycogen storage disease I and III (10), fatty acid oxidation disorders (9), disorders of amino acid metabolism (8)	Lysosomal storage disorders (28), congenital disorders of glycosilation (2)	Disorders of carbohydrate metabolism (12), glucose transporter deficiency (4)	Not applicable

Absence of significant differences among the groups.