CASE REPORT

Paediatric selective IgM deficiency and IgG4 deficiency: an extremely unusual association

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Accepted 10 August 2014

SUMMARY

Humoral immunodeficiency disorders present in children after 6 months of age with recurrent respiratory and gastrointestinal infections. These may be due to the absence of B cells causing panhypogammaglobulinaemia, or due to selective deficiencies in immunoglobulin subfractions. We present the case of a child with selective deficiency of IgM and IgG4 resulting in chronic diarrhoea and recurrent lower respiratory infections. With appropriate treatment of infections, the child had good symptom relief. Such an unusual combination of antibody deficiency has not been previously described in children. This case serves to illustrate the need for awareness to institute timely therapy for infection along with appropriate prophylactic measures like vaccination for these children.

BACKGROUND

Immunodeficiency disorders in childhood may involve defects in cellular immunity, humoral immunity or both. Humoral immunodeficiencies generally manifest in the latter half of the first year of life with recurrent sinopulmonary and gastrointestinal infections, when protective levels of maternally transmitted antibodies are no longer present. These may result from the absence or marked reduction in B-cell numbers with a resultant lack of immunoglobulins (common variable immunodeficiency), or may selectively involve specific immunoglobulin subfractions.¹

The present case describes a combined deficiency of IgM and IgG4 in a young girl resulting in chronic diarrhoea and recurrent pneumonia. Such an association is extremely unusual² and has not been previously reported in children in the literature.

CASE PRESENTATION

A 3.5-year-old girl presented with diarrhoea since 1.5 years of age (large volume, watery stools; since a month, it had also been admixed with blood and mucus). On a review of the child's history, it was found that the child also had three episodes of pneumonia in the second year of life, all requiring hospitalisation. She had empirically received antitubercular therapy for her illness, with no response. There was no history of steatorrhoea; she had no skin manifestations, abscesses or joint pains. She was not on any long-term medications.

She was born of a third-degree consanguineous marriage and was third in order of birth. Her eldest sibling was a 14-year-old girl who was alive and well. She also had an elder male sibling, who

had died at 5 years of age. This child had also had a history of recurrent episodes of diarrhoea and pneumonia since early infancy and had succumbed to one such episode.

On examination, the child was dehydrated. She had failure to thrive (weight: 8 kg, height: 77 cm; both less than fifth centile for age). The child was pale and had pitting pedal oedema; otherwise, systemic examination was within normal limits.

INVESTIGATIONS

Investigations are charted in [table 1](#). Anti-tissue transglutaminase serology was negative. Stool examination revealed the presence of oocysts of *Cryptosporidia*, trophozoites of *Giardia* and budding yeast cells of *Candida*. Colonoscopy revealed diffuse hyperaemia and ulcers in the rectum and sigmoid; biopsy from these lesions suggested active colitis, and was positive for PCR for *Cytomegalovirus*. Serology for HIV was negative. Serum total protein and albumin were 5 and 2.1 g %, respectively. Chest X-ray was suggestive of consolidation in the right upper lobe.

DIFFERENTIAL DIAGNOSIS

Recurrent diarrhoea in a young child needs consideration of coeliac disease, chronic infections like tuberculosis or HIV, milk allergy and intestinal lymphangiectasia. In addition, with a history of coexistent recurrent respiratory infections and a family history of sibling death from a similar illness, humoral immunodeficiency merits consideration.

TREATMENT, OUTCOME AND FOLLOW-UP

Initial resuscitation with intravenous fluids was followed by empiric broad-spectrum antibiotic therapy with cefoperazone-sulbactam, amikacin and metronidazole. After obtaining stool reports suggesting polymicrobial infection with *Cryptosporidium*, *Giardia* and *Candida*, nitazoxanide and fluconazole were added with continuation of metronidazole. However, diarrhoea did not resolve; by this time, colonic biopsy PCR was positive for *Cytomegalovirus*, so intravenous ganciclovir was initiated.

Workup was simultaneously initiated for an underlying immunodeficiency. Serum IgM was low; a repeat value was not detectable; however, serum IgG and IgA were normal ([table 1](#)). A possibility of selective IgM deficiency was considered. With intravenous ganciclovir, the child made a gradual recovery and was discharged from hospital after 1 month. At a follow-up visit 3 months later, she was doing well and had gained 3 kg in weight.

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To cite: Bolia R, Misra DP, Aggarwal A, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-204769

Table 1 Summary of investigations

	Reference range	September 2012	April 2013	January 2014
Age of child (year)		3.5	4	4.5
Hb (g%)	12–15	9.2	9	–
Peripheral smear		Normocytic, normochromic, no Howell jolly bodies	–	–
TLC (/mm ³)	4000–10 000	9600	13 500	–
DLC		N75L20E5	N80L17E1M2	–
ALC (/mm ³)	(>1500)	1920	2295	–
ANC (/mm ³)	(>1500)	7200	10 800	–
Absolute CD3 counts (/μL)	900–4500	–	6397	–
Absolute CD4 counts (/μL)	500–2400	–	683	–
Absolute CD8 counts (/μL)	300–1600	–	4768	–
Percentage of B cells	14–44	–	21.5	–
Percentage of NK cells	4–23	–	7.37	–
Platelet (/mm ³)	150 000–400 000	245 000	607 000	–
IgM (mg%)	50–200	27, repeat value not detectable	16	–
IgG (mg%)	490–1610	1450	1564	–
IgA (mg%)	40–200	188	175	–
IgE (IU/mL)	<100	–	1439.5	–
IgG1 (mg%)	315–759	–	1342	680
IgG2 (mg%)	61–255	–	87	78
IgG3 (mg%)	15–93	–	–	46
IgG4 (mg%)	6–26	–	<5	<5

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; DLC, differential leucocyte count; Hb, haemoglobin; NK, natural killer; TLC, total leucocyte count.

Six months after the initial admission, she presented with fever, cough and shortness of breath of 5 days duration. On examination, she was tachypnoeic and hypoxaemic. The chest X-ray revealed a diffuse reticular shadowing. Suspecting *Pneumocystis jiroveci* infection, intravenous cotrimoxazole was added to broad spectrum coverage with meropenem and vancomycin. She made a gradual recovery. Re-evaluation of immune status was conducted (table 1); serum IgG and IgA were normal, IgE was elevated and, as before, serum IgM was low. Subfractions of IgG were analysed—IgG1 and IgG2 were normal, whereas IgG4 was undetectable (<5 mg%—reference range 6–26 mg%). Absolute numbers of CD4-positive and CD8-positive T cells, and percentage of B cells and natural killer cells were all within normal limits. Isohaemagglutinin titres were low in this patient (anti-A present at 1:2 titre; expected >1:8 titre). Since the reduction of the IgG4 subfraction needed confirmation, a repeat was conducted at 3 months when the patient was not suffering from an acute illness, which reconfirmed similarly undetectable serum levels of IgG4 and low serum IgM (10 mg%). IgG3 was not done at the first instance; it was done the second time, and levels were normal. A diagnosis of selective IgM deficiency associated with IgG4 deficiency was made; at the last follow-up, the child was doing well. The child was on prophylaxis with cotrimoxazole in view of recurrent infections.

DISCUSSION

Primary selective immunoglobulin deficiencies are extremely uncommonly encountered in clinical practice. IgM antibodies are the first to form as part of the primary immune response; they have excellent complement binding property and help to clear pathogens rapidly. Selective IgM deficiency (defined as serum IgM levels usually less than 20 mg% in the paediatric age group, or less than 2 SD of age-adjusted mean serum levels), although rare by itself, has been well reported in the literature.

A review of 51 children with primary selective IgM deficiency suggested the most common presentation to be with recurrent respiratory infection (about three-fourths), including lower respiratory infections (about one-fifth) and gastrointestinal infections (about one-seventh). Other manifestations included cutaneous infections, coeliac disease and atopic disorders like asthma and allergic rhinitis. Unlike other humoral immunodeficiencies, infections with intracellular organisms like *Pneumocystis* and *Cytomegalovirus* are also described in this group of patients. Our patient had presented with respiratory and gastrointestinal disease, fitting in well with the spectrum of IgM deficiency, and also had infections with *Giardia*, *Cytomegalovirus* and *Pneumocystis* which have been previously described to affect children with this disorder. Non-specific immune abnormalities like elevated IgE levels and inversion of CD4:CD8 T-cell ratio, as was present in our patient, have been previously described in this group of patients. In contrast to adult patients with selective IgM deficiency, association with malignancy is unusual. Patients rarely need intravenous immunoglobulin replacement, and aggressive management of infections forms the cornerstone of therapy along with age-appropriate vaccination measures and maintenance of hygiene as prophylactic measures.^{3 4}

Selective deficiency of IgG4, however, is still more uncommon. The physiological role of IgG4 is uncertain. Deficiency has been reported in few patients, mostly in conjunction with IgG2 or IgA and rarely alone. It has been shown to predispose to recurrent respiratory infections and bronchiectasis.^{5–8} The combined deficiency of IgM and IgG4 has only been reported in a single adult patient with upper airway allergy, recurrent pneumonia and bronchial polyp.²

Humoral immunodeficiency should be suspected in children with recurrent chest and gastrointestinal infections; these infections should be aggressively treated. Immunoglobulin subclass deficiencies can coexist. It is essential to repeat immunoglobulin

levels at a time when the patient does not have infection to be sure of the diagnosis. Severe or life-threatening infections, if present, may need intravenous immunoglobulin therapy.

Learning points

- ▶ Humoral immunodeficiency presents after 6 months of age, with recurrent respiratory and gastrointestinal infections.
- ▶ Selective deficiency of IgM, though rare, can have a similar presentation with recurrent infections (sinopulmonary, gastrointestinal and skin) and allergic disorders.
- ▶ IgG4 deficiency is usually associated with concomitant IgG2 or IgA deficiency, and may predispose to recurrent respiratory infections.
- ▶ Concomitant IgM and IgG4 deficiency is extremely rare.

Contributors RB, DPM, AA and AS contributed to the conception and design, acquisition of data, analysis and interpretation of the data and final approval of the

version to be published. RB and DPM drafted the article. AA and AS critically revised the article for important intellectual content.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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