X-linked immune dysregulation, neonatal insulin dependent diabetes, and intractable diarrhoea

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Abstract

Four related male infants presented with neonatal diabetes mellitus, immune dysregulation with extremely high concentrations of immunoglobulin E, and intractable diarrhoea. They were all from one family, and all of them died. As far as is known this X-linked recessive disorder has not been described before.

It is suggested that this is a new immunodeficiency in which type 2 T helper responses predominate.

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We describe four baby boys from one family who presented with neonatal diabetes mellitus and intractable diarrhoea. These infants had immune dysregulation with skin rash, recurrent infections, raised immunoglobulin E (IgE) concentrations, and a fatal outcome. Review of the published findings has not revealed any previous descriptions of this apparently X-linked disorder.

Case reports

CASE 1

A boy, the proband, V-6 (fig 1), was born healthy to unrelated parents at 42 weeks gestation after an uncomplicated pregnancy. His

birthweight was 3240 g (50th centile). He had very reduced subcutaneous fat and peeling skin.

He had to be admitted to hospital at 6 weeks of age because of persistent diarrhoea, failure to thrive, and eczema. Hyperglycaemia, anaemia that was unresponsive to iron therapy, high eosinophilia and hypoproteinaemia were found. His weight was 3.77 kg (10th centile), length 54.5 cm (10th centile), and head circumference 39 cm (50th centile). He was dysmorphic with elfin facies, large mouth, and thin upper lip, and was extremely irritable and wasted. He had a widespread exfoliative skin eruption of his abdomen, groin, axillae, upper thighs and face, severe inguinal lymphadenopathy, protuberant abdomen with prominent veins, and palpable bowel loops and a patulous anus.

Insulin dependent diabetes mellitus (IDDM) was diagnosed by inappropriately low insulin (insulin 2.7 mU/l when glucose was 17.6 mmol/l) and C-peptide concentrations (C-peptide 0.06 nmol/l when glucose was 19.7 mmol/l). Stabilisation of glucose concentrations with regular subcutaneous insulin proved extremely difficult.

His diarrhoea continued without improvement despite various treatments. Stools were watery even when given total parenteral nutrition. This, together with the stool absorptive and electrolyte pattern, suggested secretory diarrhoea with a malabsorptive component. All stool cultures were negative. A jejunal biopsy specimen showed flattened mucosa with rudimentary villi. There was no crypt hyperplasia. Graft versus host disease could not be excluded from the appearance of the gut, but was not supported by other histology. A pancreatic stimulation test indicated normal bicarbonate secretion but generalised pancreatic enzyme deficiency. Sweat chloride was normal. Pancreatic enzyme replacement therapy improved his diarrhoea very slightly. Total parental nutrition was started for one month with no improvement in the diarrhoea. Enteral feeding was reinstated with an elemental infant feed, and after a few months a number of solid foods were slowly introduced into his diet. His diarrhoea never resolved completely and his weight fell to well below the third centile.

The exfoliative skin eruption partly responded to emollients and hydrocortisone cream with minimal relief obtained with antihistamines. A skin biopsy specimen showed psoriaform epidermal hyperplasia with dilated blood vessels, thick suprapapillary plates, a broad but thin layer of parakeratosis, mild spongiosis, a superficial perivascular infiltrate of lymphocytes and histiocytes and mild

Figure 1 Family tree.

Table 1 Immunological results in case 1

		10 Weeks		7 Months	
	Units	Reference range		Reference range	
Lymphocyte count	10 ⁹ /l	5.74		5.01	
<i>Lymphocyte subsets:</i>					
CD2	10 ⁹ /l	3.79	1.28–2.27	3.26	1.28–2.27
CD3	10 ⁹ /l	2.76	1.11–2.09	2.61	1.11–2.09
CD4	10 ⁹ /l	1.84	0.66–1.35	2.10	0.66–1.35
CD8	10 ⁹ /l	0.8	0.33–0.84	0.7	0.33–0.84
CD16	10 ⁹ /l	1.55	0.11–0.33	0.8	0.11–0.33
CD19	10 ⁹ /l	1.32	0.11–0.33	1.2	0.11–0.33
CD4:CD8		2.29	0.88–2.99	3.0	0.88–2.99
<i>Immunoglobulins:</i>					
IgG	g/l	4	2.0–7.0	7	3.0–8.0
IgA	g/l	0.3	<0.4	0.8	0.2–1.0
IgM	g/l	0.4	0.2–1.0	0.5	0.9–1.8
IgE	μg/l	9999	<50	40 000	<150
<i>Complement:</i>					
C3	g/l	0.5	0.9–1.8	0.5	0.9–1.8
C4	g/l	0.08	0.16–0.5	0.11	0.18–0.5
CH50	U/ml	469	520–660	629	520–660

exocytosis. Findings were not consistent with graft versus host disease. This was interpreted as erythroderma or seborrhoeic dermatitis.

Anaemia did not recur following a single blood transfusion. He had a persistent eosinophilia $0.01\text{--}3.17 \times 10^9/\text{l}$ ($0.00\text{--}0.7 \times 10^9/\text{l}$), white cell counts ranging from 6.6 to $14.7 \times 10^9/\text{l}$, and a normal bone marrow aspirate. Platelets were normal in number, size, and morphology.

He had raised plasma threonine, glutamine, and lysine and a mild increase in other amino acids; gross amino aciduria was partly overflow and partly renal in origin. He had a plasma ammonia concentration of $85 \mu\text{mol/l}$ ($20\text{--}60 \mu\text{mol/l}$) and normal lactate. Urinary vanillylmandelic acid and homovanillic acid concentrations were normal.

He had several episodes of sepsis: a septic arthritis of his left hip with associated septicaemia due to *Staphylococcus aureus*, a central line infection due to methicillin resistant *S. aureus*, and septicaemia due to group B streptococcus.

Extensive immunological investigations were performed. A thymus was present on chest x ray picture. Immunological results are summarised in table 1. He had normal lymphocyte subpopulations and CD4:CD8 ratio. CD16+ cells (natural killer cells) were high. IgG, IgA, and IgM were all within the normal range. IgE concentration was substantially increased at $5950 \mu\text{g/l}$ (<50) initially and rose to $56\ 000$. He made specific antibody to tetanus toxoid. Complement concentrations were low: C3 0.3 g/l ($0.9\text{--}1.8$), C4 0.08 g/l ($0.18\text{--}0.5$), and CH50 469 U/ml ($520\text{--}660$). He showed normal mitogenic responses to PHA (phytohaemagglutinin), PWM (poke weed mitogen), and candida antigen, mildly suboptimal response to Concanavalin A and a moderately reduced response to OKT3. An HIV antibody screen was negative. He had a normal nitroblue tetrazolium test, neutrophil migration, chemotaxis, chemiluminescence and bactericidal activity. He had pancreatic islet cell antibodies (titre 1:160), but his autoantibody screen was otherwise negative as was his rheumatoid factor. He continued to have massively enlarged inguinal lymph nodes. A

lymph node biopsy specimen showed non specific reactive change with expansion of the T zone and follicular hyperplasia.

Weekly infusions of fresh frozen plasma (FFP) were begun. The infusions seemed to improve his symptoms, particularly the secretory diarrhoea. An elemental diet (Neocate; Scientific Hospital Supplies) was continued and his condition stabilised so that he could be managed at home.

At 10 months of age, he was introduced to a branched chain amino acid supplement (Generaid; Scientific Hospital supplies), because of his continuing failure to thrive. Some 10 minutes after this feed he sustained a cardiac arrest and was dead on arrival at hospital. We believe he had an anaphylactic reaction to the formula.

Necropsy showed apparent agenesis of the islets of Langerhans, a normal exocrine pancreas, normal small bowel, generalised mild to moderate lymphoid hyperplasia and low grade and non-specific hepatitis.

CASE 2 (IV-17) (FIG 1)

This boy was born to unrelated parents at 41 weeks after an unremarkable pregnancy; he weighed 3750 g . He presented at 4 weeks of age with poor feeding, irritability, lethargy and a skin rash. Examination revealed a macular rash, tachycardia, and hepatomegaly with evidence of cardiac failure. He had no underlying structural cardiac abnormalities on echocardiogram. He responded to treatment with diuretics and digoxin. At the age of 7 weeks he developed polyuria, polydipsia, and weight loss and was found to have glycosuria, hyperglycaemia, and a low C-peptide concentration. He was given twice daily subcutaneous insulin.

Severe intractable diarrhoea developed, associated with failure to thrive. Due to the failure of all treatments, he was started on total parenteral nutrition. Attempts at enteral feeding were unsuccessful. A duodenal biopsy specimen showed shortened villi with crypt hyperplasia and increased numbers of lymphocytes and plasma cells in the lamina propria. Of particular note was the presence of large histiocytes containing periodic acid Schiff positive globules in the lamina propria and villus cores.

Hepatosplenomegaly and lymphadenopathy developed. The liver biopsy specimen was histologically normal. Electron microscopy showed large cylindrical mitochondria and prominent lipofuscin granules with glycogen rosettes throughout the cytoplasm. Similar large lipofuscin granules were seen in Kupffer cells, and there were large electron dense membrane granules in several endothelial cells. Lymph node biopsy specimens showed changes ranging from non-specific follicular hyperplasia to a florid reactive cortical hyperplasia. There was no evidence of graft versus host disease in any of the biopsy specimens.

The management was complicated by many episodes of central line infection and septicaemia. The penicillin group of drugs induced severe adverse reactions including neutropenia. Limited immune function testing

Table 2 Immunoglobulin concentrations in case 2

		6 Months	11 Months	Reference range
Units				
Immunoglobulins:				
IgG	g/l	8.7	19	3.0-8.0
IgG1	g/l	3.2		1.5-3.0
IgG2	g/l	0.82		0.3-0.5
IgG3	g/l	0.14		0.1-0.6
IgG4	g/l	0.54		<0.5
IgA	g/l	0.08	0.24	0.2-1.0
IgM	g/l	3.1	2	0.9-1.8
IgE	U/ml	1500	14500	<150
Complement:				
C3	g/l		0.63	0.9-1.8
C4	g/l		0.32	0.18-0.5

revealed normal to high concentrations of IgG, IgG subclasses, IgM and IgA with extremely high concentrations of IgE. C4 and CH50 were normal whereas his C3 concentration was slightly low. Results are summarised in table 2. Normal isohaemagglutinin antibody titres were detected. RAST tests were positive for milk. Eosinophilia occurred periodically with eosinophils comprising 0-27% of the total white cells ($0.2-53 \times 10^9/l$ (reference range 0.0-0.7)). Platelets were normal.

Ultrastructure of buffy coat preparation showed focal, membrane-bound inclusions of an homogeneous, electron dense material consistent with lipid and small amounts of lipofuscin in small lymphocytes. A rectal biopsy specimen showed lipidic and lipofuscin inclusions within fibroblasts and submucosal capillary aggregates.

At 19 months he died of overwhelming sepsis. Necropsy was not performed.

CASE 3 (IV-3) (FIG 1)

This child was born in 1961. He presented at 17 days of age with diarrhoea, restlessness, irritability, vomiting and polyuria. He had a large head and large ears. He was pale, dehydrated, tachypnoeic and wasted, with poor muscle bulk and excoriation of his buttocks and genitalia. He had pustules around a recent circumcision site. IDDM was diagnosed on the basis of glycosuria, ketonuria, and a blood glucose of 61 mmol/l. He was difficult to stabilise on insulin. He failed to thrive, and had loose watery stools.

Urine amino acid chromatography showed an increase in serine and glycine. Serum albumin and β globulin concentrations were slightly decreased and α 2 globulins and immunoglobulins were increased.

His condition deteriorated and he died at 10 weeks of age. A postmortem examination was performed and there were no macroscopic abnormalities. Unfortunately, the microscopic specimens were destroyed during processing and could not be interpreted.

CASE 4 (III-4) (FIG 1)

This child was born in 1942. There are no medical records available. He died in early infancy and was reported to have been wasted with severe diarrhoea.

Discussion

Neonatal diabetes is an extremely rare entity. Reports suggest that only 0.13% to 2.53% of juvenile IDDM presents in the first year of life, and in the neonatal period it is even rarer with only a scattering of case reports.¹⁻¹⁰ Severe intractable diarrhoea with onset in the neonatal period unrelated to an infectious cause or an established genetic abnormality is also relatively rare.^{5,11} Diarrhoea associated with an autonomic neuropathy has been described in IDDM, but is not suggested by the clinical course in the infants we have described. Several authors reporting infants with neonatal IDDM have also described severe diarrhoea.³⁻⁶ The infant described by Dourov and Buyl-Strovens³ was a girl who had steatorrhoea, malrotation, and atrophic thymus. Hattevig *et al*⁴ described a boy who was diagnosed as having IDDM and coeliac disease and responded to a gluten free diet.

Meyer *et al*⁶ described two brothers with absent islet cells, neonatal IDDM, diarrhoea and failure to thrive. One had numerous infections including fungal infections, thigh abscess, and discharging ears, and died at 4 months; the other died at 32 days, also of infection. No immunological investigations were reported. Their mother later gave birth to a healthy girl. She had 10 brothers who died of unknown causes in infancy, and a healthy sister. These infants may have had a similar entity to the infants we describe.

Two unrelated boys are described by Jonas *et al*,⁵ with neonatal IDDM and fatal secretory diarrhoea. These infants had several episodes of sepsis usually related to central venous catheters and had normal T lymphocyte subsets and T4:T8 ratios. There were some similarities in the histology of the pancreas with those of our patient, in that no islets of Langerhans were demonstrated with conventional stains, but there were also some features suggesting chronic pancreatitis which our infant did not share. In the patients described by Jonas *et al*⁵ the diarrhoea was thought to be due to mucosal dysplasia of the mid- and hindgut regions. This was not found in our patients. The small bowel histology in case 1 initially showed some flattened mucosa with rudimentary villi which had recovered by the time of his death. Case 2 also had shortened villi with hyperplasia of crypts and an abundance of lymphocytes in the lamina propria.

Powell *et al*¹² describe an interesting kindred with an X-linked syndrome with clinical features which included diarrhoea (8/19), IDDM with onset between 6 weeks and 16 years (4/19), eczematoid rashes (5/19), severe responses to viruses and immunisations (4/19) and early death (17/19). An immunological aetiology was suggested by the authors because of circulating autoantibodies in two of the three patients immunologically investigated. IgE concentrations were assessed in the three infants and was increased in only one infant (1861 U/ml). Other immunoglobulin concentrations, serum complement, and T4 counts were normal.

Several immunodeficiency disorders are characterised by chronic diarrhoea, failure to

thrive, skin rashes, recurrent infections and autoimmune phenomena. As our infants had all of these features, together with extremely high concentrations of IgE, eosinophilia, low complement concentrations, high natural killer cell numbers and pancreatic islet cell antibodies, an immunodeficiency disorder is strongly suggested. The syndrome we describe, however, does not fit into any of the recognised disorders.

Normal IgE concentrations under 1 year of age are 4 IU/ml. Yuldashev documented immunoglobulin concentrations in young insulin dependent diabetic patients and found that they had mean IgE concentrations of 171 ± 2 IU/ml which were not significantly different from concentrations in controls (50–100 IU/ml).¹³ Increased concentrations of IgE occur in a number of primary immunodeficiencies, including hyperimmunoglobulin E syndrome, Omenn's syndrome, Wiscott-Aldrich syndrome, DiGeorge syndrome, Nezelof syndrome and selective IgA deficiency (Cant A, *et al*, personal communication).^{14–16}

Hyperimmunoglobulin E syndrome, known as Job's or Buckley's syndrome, is characterised by recurrent pyogenic infections, growth retardation, coarse facies, and chronic dermatitis. It is associated with exceptionally high IgE concentrations, eosinophilia, depressed in vivo cellular immunity, with low CD8 concentrations and delayed cutaneous anergy, and variable chemotactic abnormalities of neutrophils and macrophages.^{13 15–18} Diarrhoea is not associated with hyperimmunoglobulin E syndrome nor are there any reports of associated IDDM. None of our infants had the classic facies associated with hyperimmunoglobulin E syndrome, and CD8 concentrations and chemotaxis were normal.

In 1965 Omenn described a family in which there were 12 children with widespread skin eruption (erythematous rash that progressed to an eczematoid eruption), hepatosplenomegaly, generalised lymphadenopathy, eosinophilia, poor growth and progression to death within two to six months. Other features included mild diarrhoea, secondary infections, hypogammaglobulinaemia, severe leucocytosis with eosinophilia, and mild anaemia.¹⁹ Omenn's syndrome is now a recognised clinical entity. T cell subset numbers and function may be normal, at least initially, but a loss of B cells, a decline in IgG, IgA, and IgM with raised IgE concentrations ensues and there is prominent lymphocytic, eosinophilic, and histiocytic infiltration of skin, gut, bone marrow and lymph nodes.^{14 15 20} It is thought that there is deregulation of T lymphocyte subsets with functional T cell suppression of immunoglobulin production and reduced B cell populations.^{14 15} Fischer (1993) postulates that the T cell infiltrate result from autoimmune specificity of these cells in a context of defective negative selection.²⁰

The infants we have described share several features with Omenn's syndrome: the widespread skin eruption, generalised lymphadenopathy, diarrhoea, infections, eosinophilia and raised IgE concentrations. IDDM has

not been described in children with Omenn's syndrome and our infants showed no deterioration in either B cell numbers or immunoglobulin concentrations. Lymphocytic and histiocytic infiltration was seen in biopsy specimens. Eosinophilic infiltration, as described in Omenn's syndrome, was not observed.

Buckley and Sampson¹⁴ suggested that immunodeficiencies with raised IgE concentrations have abnormalities of thymus dependent immune function. In none, however, is T cell function definitely absent, and they go on to suggest that there may be sufficient T helper cells to initiate IgE antibody formation but an inadequate number of suppressor cells, resulting in augmented IgE synthesis.

The differential function of cytokines by T helper cells during an immune reaction and the regulatory effects on the nature of the response could suggest that these disorders may in fact share cytokine abnormalities. Interferon α (IFN α) and IL12 produced by macrophages following stimulation by viruses and intracellular bacteria, together with interferon γ (IFN γ) produced by natural killer cells (NK) and T cells, induce type 1 T helper reactions.²¹ On the other hand, absence or low concentrations of IFN γ and the presence of IL4 seems to be critical for the development of type 2 helper responses in which the production of IL4 and IL5 predominates and promotes the production of IgG1 and IgE secreting cells and eosinophilia.²¹ In these disorders there is either an inadequate response to stimulation to produce sufficient IFN γ to block type 2 responses, or activated lymphocytes produce inappropriate amounts of IL4 or IL5 which promotes type 2 responses preferentially.

The apparent improvement seen in case 1 when given fresh frozen plasma may have been due to correction of a cytokine imbalance. High NK cell numbers were shown, but unfortunately IFN γ concentrations were not measured.

The pedigree described shows X-linked recessive inheritance. The only other form of inheritance that requires serious consideration is mitochondrial inheritance and this seems unlikely given that only boys are affected and a large number of girls who must have the mutant gene remain unaffected. DNA linkage studies are currently being done.

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