

## CASE REPORT

# Anhidrotic ectodermal dysplasia and immunodeficiency: the role of NEMO

E D Carrol, A R Gennery, T J Flood, G P Spickett, M Abinun

Arch Dis Child 2003;88:340-341

Anhidrotic (hypohidrotic) ectodermal dysplasia associated with immunodeficiency (EDA-ID; OMIM 300291) is a newly recognised primary immunodeficiency caused by mutations in *NEMO*, the gene encoding nuclear factor  $\kappa$ B (NF- $\kappa$ B) essential modulator, NEMO, or inhibitor of  $\kappa$ B kinase (IKK- $\gamma$ ). This protein is essential for activation of the transcription factor NF- $\kappa$ B, which plays an important role in human development, skin homeostasis, and immunity.

We present an update on the first reported patient with EDA-ID syndrome<sup>1</sup> subsequently shown to be caused by *NEMO* mutation,<sup>2</sup> and our current understanding of this rare primary immunodeficiency.

Immunodeficiency is an important feature of many rare congenital and hereditary conditions involving multiple organs and systems<sup>3</sup> (for example, IPEX—immunodeficiency, polyendocrinopathy, enteropathy, X linked; ICF—immunodeficiency, chromosomal instability, facial anomalies; Netherton syndrome, Schimke immuno-osseous dysplasia, etc). For many of these conditions underlying gene mutations have been recently identified, leading to our better understanding of functions of the immune system. From the practical point of view, recognising that immunodeficiency is part of the broader syndrome is important as the majority of care of these rare and complex patients is supervised locally by general paediatricians. Understanding of the interrelation of the problems these patients face allows previously unrecognised complications to be actively sought and treated.

### CASE REPORT

We previously described a 4 year old white boy with clinical features of X linked anhidrotic ectodermal dysplasia who suffered from recurrent life threatening infections caused by

*Streptococcus pneumoniae*. We found that he had associated specific antibody deficiency (SPAD), in particular antipolysaccharide antibody deficiency.<sup>1</sup> He initially responded well to intravenous immunoglobulin (IVIg) replacement, but as one of the possible explanations for his SPAD was a maturational delay of the immune system, this was stopped after two years and his specific antibody production was reassessed. The original diagnosis was confirmed, as well as low IgG2 subclass level and very low specific antibody response to tetanus toxoid. He was recommenced on IVIg replacement, and at follow up at age 11 years he has remained free of major infections with no evidence of bronchiectasis on high resolution chest computerised tomography (CT) scanning. However, his serum IgA remains very high and that of IgM is declining, suggestive of ongoing immune dysregulation (table 1).

### DISCUSSION

The classification of ectodermal dysplasias has been recently reviewed, and over 150 distinct phenotypes identified based on presentation of abnormal teeth, skin, nails, sweat glands, and hair.<sup>4</sup> After our first report, more than 20 patients have been described with features of immunodeficiency associated with X linked anhidrotic ectodermal dysplasia not caused by mutations in *ED1* gene causing the common X linked form. These unrelated patients, including ours, were shown to have mutations in *NEMO*, the gene coding for a molecule with important functions in the NF- $\kappa$ B signalling pathway.<sup>2,5</sup>

The EDA-ID syndrome is clinically heterogeneous; the main features are somewhat milder than those of "classical" anhidrotic ectodermal dysplasia (hypo- or anodontia with conical shaped maxillary incisors, dry skin with hypo- or anhidrosis and hypo- or atrichosis). However, some children manifest a more severe phenotype with osteopetrosis and lymphoedema (OL-EDA-ID; OMIM 300301).<sup>6</sup> The immunodeficiency, of which the impaired antibody response to polysaccharide antigens is the most consistent laboratory feature, is severe with

**Table 1** Serum immunoglobulin, IgG subclass, and specific antibody levels

	Pre-IVIg		On IVIg	Off IVIg	On IVIg		Age related reference range
	12/'93	05/'94	08/'95	09/'96	12/'96	10/2001	
IgG	12.4	10.8	12.0	9.29	10.6	9.81	3.8–15.2 g/l
IgM	0.55	0.48	0.51	0.36	0.48	0.31	0.43–1.90 g/l
IgA	7.33	4.53	4.18	4.20	5.14	9.51	0.64–2.58 g/l
IgG <sub>1</sub>	9	9		7.82			2.3–6.4 g/l
IgG <sub>2</sub>	0	1.2		0.15			0.7–4.5 g/l
IgG <sub>3</sub>	0.53	0.54		0.81			0.1–1.0 g/l
IgG <sub>4</sub>	0	0.15		9.0			0–0.8 g/l
IgE	<2			<2			0–56 kU/l
Specific ab to:							
Tetanus	<0.25	0.47		<0.08	0.09		>0.1 IU/l
Hib*	<0.15	<0.15		<0.10	0.54		>1 $\mu$ g/ml
Pneumococcus†	<2	<1		1	<1		>20 U/ml

\*Haemophilus influenzae type b tetanus conjugate vaccine—04/1994, repeated 09/1996.

†Polyvalent pneumococcal polysaccharide vaccine (Pneumovax II)—02/1994, repeated 09/1996.

significant morbidity and mortality. From early childhood, affected boys suffer from unusually severe, life threatening, and recurrent bacterial infections of lower respiratory tract, skin and soft tissues, bones, and gastrointestinal tract, meningitis, and septicaemia, leading to bronchiectasis, chronic lung disease, intractable diarrhoea, and failure to thrive. The commonly implicated pathogens are *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas* species, *Haemophilus influenzae*, and mycobacteria. A number of reported children have died with disseminated mycobacterial infections. Replacement IVIg, antibiotic treatment and prophylaxis, and avoiding live vaccines, especially BCG, are the current management guidelines; bone marrow transplantation has been attempted in one patient.<sup>6</sup>

EDA-ID is inherited as an X linked recessive trait; the female relatives of affected boys may have variable clinical features such as dry and/or hyperpigmented skin, hypodontia, conical teeth, and sometimes increased serum IgA. Indeed, our patient's mother has conical teeth. Interestingly, a female patient with features of EDA-ID and a heterozygous hypomorphic *NEMO* mutation has recently been reported.<sup>7</sup>

Functional NEMO is essential for activation of the transcription factor NF- $\kappa$ B, which is involved in inducing immune and inflammatory responses; it is important for normal T and B cell development, as well as osteoclast function, skin epidermal cell growth, and maintenance of the vessel architecture. Its targets include genes that produce antiapoptotic factors, cell adhesion molecules, cytokines, and chemokines.<sup>5</sup> The "loss of function" *NEMO* mutation causes incontinentia pigmenti (IP), where the consecutive lack of NF- $\kappa$ B activation results in extreme susceptibility to apoptosis, leading to embryonic death in males, and explains the extremely skewed X inactivation seen in females. Finding of hypomorphic *NEMO* mutations in patients with allelic syndromes of EDA-ID and OL-EDA-ID suggests that the milder phenotype in affected males and both random and skewed X inactivation seen in female carriers are the result of only partial loss of NEMO function.<sup>2-5</sup>

Both the phenotype-genotype correlation of patients with EDA-ID and the importance of hypomorphic *NEMO* mutations in disturbed pathways of primarily innate and possibly acquired immunity are currently being investigated.

#### ACKNOWLEDGEMENT

We are grateful to Professor J-L Casanova for collaboration, support, and encouragement.

#### Authors' affiliations

**E D Carrol, A R Gennery, T J Flood, M Abinun**, Department of Paediatric Immunology, Newcastle upon Tyne Hospitals NHS Trust, Newcastle upon Tyne, UK

**G P Spickett**, Regional Immunology Department, Newcastle upon Tyne Hospitals NHS Trust

Correspondence to: Dr M Abinun, Department of Paediatric Immunology, Newcastle upon Tyne Hospitals NHS Trust, Newcastle upon Tyne NE4 6BE, UK; mario.abinun@ncl.ac.uk

Accepted 10 October 2002

#### REFERENCES

- 1 **Abinun M**, Spickett G, Appleton AL, *et al*. Anhidrotic ectodermal dysplasia associated with specific antibody deficiency. *Eur J Pediatr* 1996;**155**:146-7.
- 2 **Doffinger R**, Smahi A, Bessia C, *et al*. X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF- $\kappa$ B signalling. *Nat Genet* 2001;**27**:277-85.
- 3 **IUIS Scientific Group**. Primary immunodeficiency diseases. *Clin Exp Immunol* 1999;**118**(suppl 1):1-28.
- 4 **Priolo M**, Lagana C. Ectodermal dysplasias: a new clinical-genetic classification. *J Med Genet* 2001;**38**:579-85.
- 5 **Aradhya S**, Nelson DL. NF- $\kappa$ B signalling and human disease. *Curr Opin Genet Develop* 2001;**11**:300-6.
- 6 **Dupuis-Girod S**, Corradini N, Hadj-Rabia S, *et al*. Osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia, and immunodeficiency in a boy and incontinentia pigmenti in his mother. *Pediatrics* 2002;**109**:e97.
- 7 **Kosaki K**, Shimasaki N, Fukushima H, *et al*. Female patient showing hypohidrotic ectodermal dysplasia and immunodeficiency (HED-ID). *Am J Hum Genet* 2001;**69**:664-5.