

RESEARCH LETTER

WILEY

Poor head growth and developmental delay in infants with eczema, food allergies and growth faltering

To the Editor,

Early-onset, moderate-to-severe eczema in infants is associated with food allergy in 30–65% and faltering growth in infancy.¹ We observed poor head growth and developmental delay in severely affected infants and conducted a retrospective case review to compare clinical and laboratory features between infants with severe eczema, food allergy/sensitisation and faltering growth with restricted head growth (*cases*) and those with similar clinical presentation but preserved head growth (*comparator/control group*).

A clinical database search (Paediatric Allergy Service, St Mary's Hospital, London UK) for the period 2002–2011 was undertaken with the search terms: 'growth-faltering/failure', 'poor weight gain', 'failure to thrive', 'malnutrition' and 'stunting'. The hospital review and audit board approved the study. Inclusion criteria were age < 18 months at presentation; severe eczema, faltering growth, food allergy/sensitisation. Exclusion criteria were insufficient data available to determine infants' growth pattern. Records were examined independently by two paediatricians (EM/CG). Neurodevelopmental delay was diagnosed if neurological examination by >1 certified/senior paediatrician showed that age-appropriate developmental milestones were not achieved. Eczema was diagnosed and severity determined by the degree of skin involvement, sleep disturbance, need for admission and potent topical corticosteroids. Food allergy was diagnosed based on a history of rapid reaction on exposure to food with corroborating positive specific IgE (ImmunoCAP; Phadia, Uppsala/Sweden; ≥ 0.35 kU_A/L considered positive) or skin prick tests (Stallergenes, France; wheal diameter of ≥ 3 mm above saline control considered positive) and/or tests exceeding previously published 95% threshold values for reactivity. Test-positive foods which failed to fulfil the above criteria were initially avoided and subsequently introduced by supervised oral food challenge. Elimination diets were supervised by experienced paediatric dietitians. Weight, height and occipital-frontal head circumference (OFC) were measured according to accepted standards and documented on sex-specific United Kingdom Growth Charts. Dietetic and personal child health records yielded additional measurements. Weight and OFC measurements were converted into z-scores using WHO Anthro (3.2 WHO, 2006), and definitions for moderate malnutrition of < -2 z-scores were used.²

Growth faltering was defined as a change in weight-for-age of > -1 z-score in a 3-month period in infants less than 1 year of age. In children over 1 year of age, growth faltering was defined as inadequate growth or weight gain ≥ 1 month in a child under 2.² Moderate nutritional deficit was defined as > -2 z-scores using World Health Organisation criteria.³ Nutrition rehabilitation was considered to have been achieved when weight-for-age and OFC-for-age were > -1 z-score. Other study terminology included *pre-diagnosis* z-scores, highest z-score recorded prior to clinical presentation; *diagnosis (acute)* z-scores, taken at the time of clinical presentation and allergy diagnosis; *convalescent* z-scores, taken 4–60 weeks after initiation of allergen-exclusion measures. Cases were defined as infants with ≥ 0.67 standard deviations decrease in OFC-for-age z-score and/or increase in OFC-for-age z-score following the institution of a hypoallergenic diet. Controls were defined as infants with a decrease of ≥ -1 weight-for-age z-score over a period of 3 months and maintained OFC-for-age z-scores. The chi-square test was used to compare categorical variables and nonparametric analysis for continuous variables (SPSS version 15.0; SPSS Inc, Chicago, IL, USA). Interpretation of analyses took account of the number of comparisons made, but formal correction for multiple comparisons was not used.

We identified 65 infants aged < 18 months with documented faltering growth, severe eczema and multiple food allergy/sensitisation. OFC was recorded for 43/65 (66.2%), and sufficient growth data were available for 16/43 (37.2%). 15/16 infants presented to the emergency department from the community; one to the allergy service. All infants exhibited faltering growth with a severe decrease in weight-for-age at presentation (median z-score -2.13 [IQR -2.74 to -1.22]; range -1.01 to -4.62). Nine infants (56%) had restriction of head growth (*cases*) with decreased OFC-for-age (median z-score -1.12 [IQR -1.29 to -0.63]; Figure 1A,B). There was no difference between cases and controls for demographics, family history of atopy, feeding practice, age of eczema onset, age at presentation or disease duration or weight-for-age z-scores at diagnosis (Table 1).

Cases exhibited a greater decrease in weight-for-age z-score between pre-diagnosis and diagnosis (median -2.46 [IQR -2.97 to -1.67], range -4.62 to -1.22) compared with controls (median -1.28 [IQR -2.24 to -1.08], range -2.4 to -1.01); $p = .037$. After treatment

with elimination diet, amino acid formula and hypoallergenic complementary foods the OFC-for-age z-scores increased significantly more in cases (median 1.15 [IQR 0.88–1.38], range 0.28–1.83) compared with controls (median –0.13 [IQR –0.14 to 0.11], range –0.32 to 0.67); $p = .001$ (Figure 1C–E).

Infants in both groups displayed sensitisation to multiple foods (median 8, range 3–15), mostly without prior history of ingestion. Half of the infants presented with hypoalbuminaemia (median 30; range 19–44 g/L; normal 35–50) and hypogammaglobulinaemia (median 2.45 g/L, range 1–8.7; normal 3.1–15.8). No significant differences between cases and controls were observed for serum total IgE, albumin, total protein, total globulin, haemoglobin, counts of leukocytes, platelets (thrombocytosis common), neutrophils, eosinophils and lymphocytes. Compared with controls, cases had higher levels of circulating specific IgE to soya and wheat, as well as higher neutrophil percentage of total leukocyte count. Eosinophil percentage was high in both groups (Table 1).

Five infants exhibited neurodevelopmental delay at presentation (2/5 motor delay with significant hypotonia, 3/5 global developmental delay, predominantly motor with hypotonia) and all had restricted head growth. They had more severe growth faltering with a larger difference in weight-for-age z-scores between pre-diagnosis and diagnosis compared with developmentally normal infants (median –2.79 [IQR –4.17 to –2.31] vs. –1.39 [–2.28 to –1.06]; $p = .038$). Developmental delay was not associated with gastrointestinal symptoms, age of eczema onset, age at presentation nor disease duration.

Introduction of dietary and skin treatment led to the control of eczema, gastrointestinal symptoms and rapid catch-up growth in all infants (Figure 1). Inflammatory parameters returned to normal, with only mild eosinophilia persisting in most infants. Cases had a significantly higher z-score increase in convalescent OFC-for-age compared with controls and improvement in weight-for-age z-scores on treatment was higher for cases than controls (Figure 1C). Infants with feeding aversion ($n = 4$ cases, $n = 4$ controls) had lower weight-for-age z-score increases post-treatment. Neurodevelopmental sequelae persisted for 3/5 children for ≥ 24 months.

Severe eczema and multiple food allergies are known to cause growth faltering in infancy and can be associated with allergic gastrointestinal inflammation.^{1,4} The assumption hitherto has been that head growth is maintained as occurs with other malnutrition states. To our knowledge, this is the first description of restricted head growth with associated developmental delay in young infants presenting with severe, multisystem allergic disease, raised inflammatory parameters and multiple food allergy/sensitisations whilst being exclusively or predominantly breastfed.

Poorer growth in children with food allergies and eczema is recognised,⁴ and negative impact on weight, height, body mass index and head circumference, but not neurodevelopmental progress, has been described.⁵ Allergic inflammation may contribute to growth failure⁴ and it has been linked with lower neuropsychological

Key messages

- Severe infantile eczema and multiple food allergy can cause faltering growth and systemic allergic inflammation.
- We describe restricted head growth and developmental delay in infants with eczema and food allergy.
- Timely management of infants with multisystem allergy may prevent adverse physical and developmental outcomes.

function, albeit within the normal range of development.⁶ Other chronic inflammatory conditions such as juvenile arthritis, inflammatory bowel disease and Crohn's disease can lead to growth faltering in children with decreased weight gain and height velocity but not with cerebral effects and head growth tends to be preserved.⁷ Cessation of head growth has been described in young children with chronic renal failure who displayed some additional developmental delay.⁸ This was attributed to nutritional and inflammatory aberrations and appeared to improve post-transplantation. Long-term follow-up is needed, as growth faltering at 6–8 weeks of life is associated with developmental delay and poor growth can impact negatively on cognitive ability and socio-economic activity in adulthood.⁹

We hypothesise that systemic allergic inflammation may have profound effects on the brain in some infants and may lead to reduced brain growth until the inflammation is controlled.

This retrospective case review relied on data obtained at clinical presentation and from records, without formal eczema or growth assessment at predefined time points. We only included infants for whom extensive clinical data were available and defined growth faltering and restricted head growth according to accepted criteria.³ In this retrospective study, we could not exclude specific genetic syndromes; however, neither clinical features nor progress of our cohort were typical of these.

Multiple statistical testing was performed to identify whether there were differences in sensitisation or overall inflammatory patterns. We interpreted the findings with caution but believe them to be important as the basis of future hypothesis development and study of underlying mechanisms.

Young infants with severe eczema and food allergies are at risk of growth faltering. We describe a new phenotype in this spectrum, with restricted head growth and neurodevelopmental delay. Our data support the importance of early recognition and treatment of food allergy in infants who present with severe eczema and growth faltering, and close monitoring of head growth and developmental outcomes, as well as early diagnosis and treatment of severely allergic infants. Delayed institution of topical anti-inflammatory

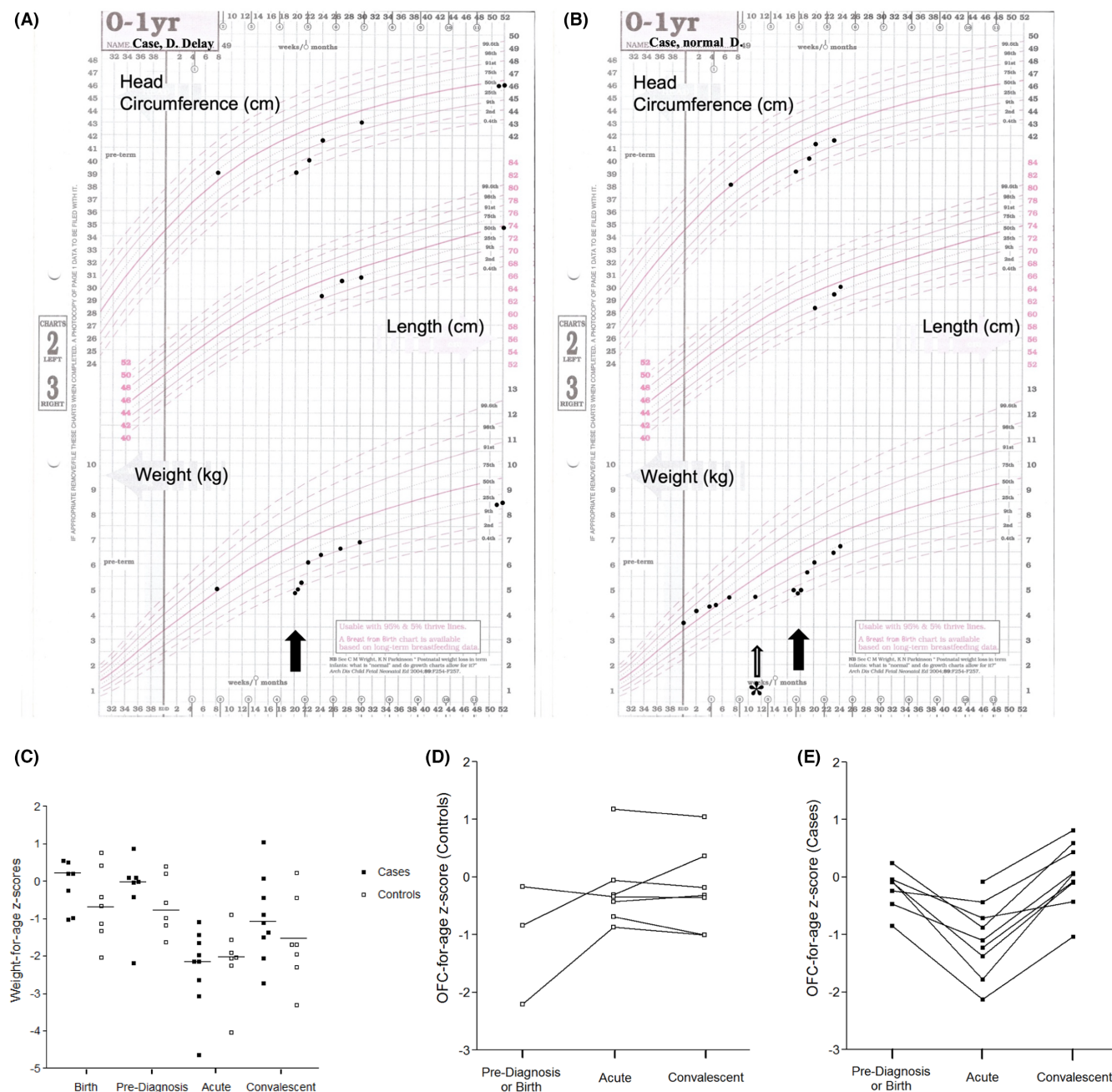


FIGURE 1 Growth of infants with severe eczema, growth faltering and allergic sensitisation to foods. Data demonstrate growth faltering and restricted head growth and their response to elimination diet. (A) infant with restricted head growth and developmental delay. (B) infant with restricted head growth and normal development. Solid Arrow, amino acid formula/elimination diet commenced; *Arrow, emergency department attendance. (C) differences in weight-for-age z-scores between cases and controls at relevant time points. (D) OFC-for-age z-scores, controls. (E) OFC-for-age z-scores, cases. OFC, occipitofrontal head circumference (Growth chart reproduced with permission: Royal College of Paediatrics and Child Health DoH WHO. United Kingdom Growth Chart. 2009. Department of Health, United Kingdom.)

TABLE 1 Differences between cases and controls for demographic details, feeding history, clinical presentation and treatment.

	Cases n = 9	Controls n = 7	p-value ^a
Demographics			
Gender (female %)	5 (56%)	5 (71%)	0.63
Family history of atopy	7 (78%)	5 (71%)	1.0
Family history of eczema	4 (44%)	2 (29%)	0.62
Firstborn	7 (78%)	5 (71%)	1.0
Ethnicity			
Asian	1	3	–
Black African	1	0	
White	2	1	
Mixed Race	3	2	
Chinese	2	1	
Age eczema started, weeks, (Median [IQR], Range)	5 [3.3–11], 2–12	8 [4–12], 3–20	0.34
Age at presentation, weeks, (Median [IQR], Range)	21 [17–31], 16–60	23 [20–31], 17–31	0.56
Eczema duration at presentation (weeks, median [IQR], Range)	15.5 [10–18], 4–32	17 [9–22], 3–23	0.82
Feeding history			
Breastfed ever	All	All	
Breastfed at diagnosis			
Exclusive (= no other type of milk)	5 (56%)	5 (71%)	1.0
Std Formula top-up	2 (22%)	–	
Maternal dietary restrictions during breastfeeding	5 (62.5%)	4 (57%)	1.0
Exposed to standard formula ever (including first attempt only)	4 (44%)	3 (43%)	1.0
Extensively hydrolysed formula tried prior to amino acid formula	0	1 (14%)	0.44
Weaned onto amino acid formula from exclusive breastfeeding	5 (56%)	3 (43%)	0.62
On complementary foods at time of diagnosis	6 (67%)	6 (86%)	0.59
Specific complementary foods already avoided at time of diagnosis	6 (67%)	4 (57%)	1.0
Clinical findings and treatment at presentation			
Eczema severe	9	7	–
Gastrointestinal symptoms	8 (89%)	4 (57%)	0.26
Aversive feeding behaviour documented	4 (44%)	4 (57%)	1.0
Developmental delay	5 (44%)	0	0.044
Antihistamine, oral	2 (22%)	1 (14%)	1.0
Respiratory symptoms	1 (11%)	1 (14%)	1.0
Number of food allergies^a			
≤1	–	–	–
2	–	1	
3	2 (11%)	0 (14%)	
4	1 (11%)	0 (14%)	
5	2 (33%)	1 (29%)	
6	2 (45%)	5 (43%)	
Significant comorbidities at diagnosis	1 = renal tubular acidosis and rickets ^b	–	–
<i>Staphylococcus aureus</i> isolated on skin swab	4/6	5/7	–
Antibiotics commenced	4/9 (44%)	3/7 (43%)	1.0

TABLE 1 (Continued)

	Cases <i>n</i> = 9	Controls <i>n</i> = 7	<i>p</i> -value ^a
Topical steroid potency			
Potent	6 (67%)	6 (86%)	0.21
Moderate	3 (33%)	0	
Mild	0	1 (14%), on calcineurin inhibitor	
Hospitalised at presentation	9 (100%)	6 (86%) one ambulatory	0.44
Amino acid formula commenced	All	All	–
Key laboratory findings at presentation	<i>n</i> /9 (tests done/available) Median [IQR], Range	<i>n</i> /7 (tests done/available) Median [IQR], Range	
Immunoglobulin E (IgE), total	6/9 1734 [571.3–4283.5], 62–5410	6/7 800 [96.8–1096.8], 90–1105	0.15
Immunoglobulin G	9/9 4.2 [1.6–7.05], 1–8.7	3/7 1.9 [1.7–2], 1.7–2	
Immunoglobulin A	9/9 0.3 [0.26–0.5], 0.2–0.6	3/7 0.1 [0.1–0.2], 0.1–0.2	
Immunoglobulin M	9/9 0.6 [0.3–0.95], 0.18–1.2	3/7 0.2 [0.2–0.6], 0.2–0.6	
IgE Cow's Milk (kUA/L)	9/9 29.8 [2.8–72.3], 0.1–100	7/7 62.4 [2.5–100], 0.51–100	0.71
IgE Egg (kUA/L)	8/9 38.5 [10.4–89.3], 1.6–100	7/7 67.9 [7.4–90.3], 0–100	0.70
IgE Soya Bean (kUA/L)	9/9 24.6 [1.33–49.9], 0.1–100	5/7 0.67 [0–3.82], 0–6.75	0.042
IgE Wheat (kUA/L)	8/9 74.5 [34–100], 0.7–100	6/7 15.8 [1.05–37.3], 0–52.1	0.027
Complete blood count	9/9	7/7	
Platelet count	538 [421–687], 354–844	374 [273–580], 229–617	0.13
Total leukocyte count	17.6 [10.6–23.8], 6.8–38.7	16.6 [13.0–18.8], 11.3–21.4	0.95
Lymphocyte % of total leukocyte count	45.7 [43.4–62.2], 25.6–68.2%	48.4 [44.2–69.4], 43.6–75.2	0.56
Eosinophil % of total leukocyte count	11.8 [6.8–27.2], 0.5–28.6	19 [11.8–29.1], 5.3–30.7	0.32
Neutrophil % of total leukocyte count	22.7 [17.5–35.7], 11.8–64.8	13.4 [6.9–20.3], 3.6–25	0.045

^aChi-square/Fisher's exact (categorical variables); nonparametric MWU/exact test (noncategorical variables);

^bResolved after supplementation and exclusion diet.

treatment and appropriate, supervised allergen-exclusion diets may result in adverse neurodevelopmental outcomes.

DATA AVAILABILITY STATEMENT

Data can be made available on request.

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FINANCIAL DISCLOSURE

All authors of this manuscript declare that they have no relevant financial disclosures.

AUTHOR CONTRIBUTIONS

HC and CG identified the clinical pattern and conceived the study design. CG, EM and LM collected, reviewed and analysed the data. All authors contributed to the manuscript.

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KEYWORDS

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Claudia Gore¹ 

Eleanor Minshall²

Luise V. Marino^{3,4}

Helen Cox¹

¹Department of Paediatric Allergy, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK

²Department of Paediatric Allergy, Sheffield Children's NHS Foundation Trust, Sheffield, UK

³Department of Paediatric Intensive Care Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK

⁴Faculty of Health Science, University of Southampton, Southampton, UK

Correspondence

Claudia Gore, Department of Paediatric Allergy, St Mary's Hospital, The Bays Building, Praed Street, London W2 1NY, UK.

Email: cgore@nhs.net

ORCID

Claudia Gore  <https://orcid.org/0000-0002-3626-5129>

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