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Allergic disease in the first year of life is associated with differences in subsequent neurodevelopment and behaviour

Suzanne J. Meldrum [a,b,*], Nina D'Vaz [a], Janet A. Dunstan [a], Trevor A. Mori [c], Kathryn Hird [a,d], Karen Simmer [a,b], Susan L. Prescott [a]

[a] School of Paediatrics and Child Health, University of Western Australia, Perth, Australia
[b] School of Women's and Infants Health, University of Western Australia, Perth, Australia
[c] School of Medicine and Pharmacology Royal Perth Hospital Unit, University of Western Australia, Perth, Australia
[d] Faculty of Medicine, Notre Dame University, Fremantle, Australia

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ABSTRACT

Background: Recent trials suggest a link between neuropsychological function, atopy and allergic disease particularly in early childhood; however the nature of this association remains unclear.
Aims: To investigate the relationship between early allergic disease and sensitisation at 12 months of age and neurodevelopmental outcomes at 18 months.
Study design: Linear or binary logistic regression analysis was used to determine whether allergic diseases or sensitization at 12 months of age was a significant predictor of neurodevelopmental test scores at the 18 months.
Subjects: Infants with a maternal history of allergic disease (n = 324).
Outcome measures: Allergic outcomes at 12 months of age included allergen sensitisation, eczema, IgE-mediated and food allergy, and neurodevelopmental outcomes at 18 included the Bayley Scales of Infant Toddler Development III Edition, the Achenbach Child Behaviour Checklist and the Macarthur Scales of Infant Toddler Development.
Results: Children with any diagnosed allergic disease at 12 months had evidence of reduced motor scores ($p = .016$), and this was most apparent for a diagnosis of eczema ($p = .007$). Non-IgE mediated food allergy was significantly positively associated with problem Internalising Behaviours ($p = .010$), along with a trend for effects on the Social–Emotional composite score for IgE-Mediated food allergies ($p = .052$). Allergic sensitisation was not independently associated with any effects on neurodevelopmental outcomes.
Conclusion: This study provides evidence that an allergic phenotype in infancy is associated with effects on neurodevelopment. Further research is required to investigate the nature of this relationship.

1. Introduction

While a link between the nervous system and the immune system is recognised, it is still not well understood, particularly in early life when these critical systems are developing. However, growing epidemiological data suggests complex and bi-directional interactions between neuropsychological wellbeing and immune disorders [1], which are increasingly relevant with the dramatic rise in inflammatory immune diseases such as allergy and autoimmunity. This has been better studied in adults, where, on one hand, psychological factors have been associated with triggering the onset/exacerbation of atopic disorders [2–5], and on the other hand, the development of atopic disorders is linked to disruption in performance and cognitive abilities [6–8] and anxiety and depression [9,10]. In children these interactions appear even more complex, but supported by associations between allergic disease, specifically eczema, and ADHD [11–15], other specific mental health disorders [16–19] and temperament [20], particularly in children with asthma [21–23]. There are several major hypotheses attempting to explain the associations between allergy and neurobehaviour [1].

Firstly, that allergic symptomatology may adversely affect neurodevelopment as a consequence of the clinical manifestations and necessary treatments [24]. Secondly, that the parental stress/anxiety towards raising a child with an allergic disease may alter the home environment and interaction with the child significantly enough to alter child behaviour or performance [25,26].

And lastly, an altered physiological response to stress or other adverse event (acute or chronic) during early development may adversely affect both the immune and central nervous systems through effects on the stress response of the hypothalamic–pituitary–adrenal

* Corresponding author at: School of Paediatrics and Child Health Research, University of Western Australia, Perth, Australia, PO Box D184, Princess Margaret Hospital, Perth WA 6001, Australia. Tel.: +61 8 9340 8340; fax: +61 9388 2097.
E-mail address: smeldrum@meddent.uwa.edu.au (S.J. Meldrum).

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system (HPA). Chronic stress has been associated with increased circulating levels of inflammatory cytokines, and increased inflammatory responses at birth (IL-6, TNFα and IL-1β). In newborns, allergic predisposition (allergic heritage and elevated cord blood IgE) is associated with increased cortisol levels after a stressor (heel prick blood sampling) suggesting altered HPA axis response to stress [27]. In addition, studies of children have observed a general association between HPA axis dysregulation and behaviour [28], with elevated cortisol levels associated with alterations in emotion regulation [29], psychotic symptoms [30] and clinical depression [31,32].

Collectively these observations support the notions that there are important and intricate neuro-immune interactions in very early development that have the capacity to shape subsequent function. To our knowledge this is the first study to examine the relationship between an emerging allergic phenotype in the first year of life and early neurodevelopment.

2. Methods

2.1. Study population

The study population included 420 healthy term infants participating in a study to investigate the effects of early dietary exposures on allergic outcomes and neurodevelopment, as described elsewhere [33]. Briefly, Western Australian women with confirmed allergic disease were recruited during the third trimester of pregnancy. Maternal atopy was defined by a history of allergic disease and at least one positive skin prick test to one of a defined panel of allergens. After delivery infants were randomised at birth to receive either a high dose DHA-enriched fish oil supplement, aimed at delivering approximately 250 mg of DHA per day (n = 218) or a placebo containing olive oil (n = 202). As will be published elsewhere, this intervention had no effect on allergic outcomes, or key indicators of neurodevelopment as assessed by the Bayley Scales of Infant Development—3rd Edition (BSID-III), it was nonetheless examined as a confounding factor in this analyses of the present study. This study was approved by Princess Margaret Hospital Research and Ethics Committee. Written informed consent was obtained from all subjects before enrolment.

2.2. Allergy and immune assessments

The primary allergic outcomes were assessed at 12 months of age. Parents completed questionnaires to document any symptoms, diagnosis and treatment of allergic disease. Children were skin prick tested (SPT) to a panel of common allergens, clinically assessed for eczema and blood was collected. The clinical history (questionnaire information), clinical assessments (including SCORAD index), and SPT results were assessed by a paediatric immunologist to obtain a clinical diagnosis of confirmed allergic disease. The SPT included common allergen extracts (milk, peanut, house dust mite, cat, grass, mould; Hollister-Stier Laboratories, Spokane, WA, USA), whole egg, histamine (as a positive control) and glycerine (as a negative control). A wheal diameter of ≥2 mm was considered positive. A diagnosis of clinical allergic disease was further categorised according to published clinical guidelines [34] and included:

- Food Allergy; IgE Mediated/Non-IgE Mediated:

IgE-mediated food allergy was defined as a history of immediate symptoms (typically angioedema, urticaria, respiratory or gastrointestinal symptoms within 60 min) following contact with and/or ingestion of food and associated with a positive SPT to that food. Non-IgE mediated food allergy was defined as reactions to foods (typically gastrointestinal upset or non-urticarial skin rashes) which appear to be associated with ingestion of specific foods (typically >2 h) but with no evidence of IgE sensitisation to that food.

- Eczema

A diagnosis of eczema was made in infants with typical skin lesions [35], and the severity documented by the SCORAD index [36]. The extent and severity of lesions "on the day" of assessment were documented by researchers and parents provided subjective scores for itch and sleep disturbance. The same scoring system was used to collect data on the extent and severity of eczema when it was "at worst" in the preceding months since the first visit. This was done by parent reporting of surface area affected and the use of the SCORAD manual and a pictured scale (photographs) for each severity criterion.

- Asthma

A diagnosis of asthma was based on a history of recurrent wheeze with responsiveness to bronchodilator medications.

- Allergic rhinoconjunctivitis

Allergic rhinitis and/or allergic rhinoconjunctivitis was diagnosed by typical symptoms (recurrent nasal congestion, itching rhinorrhoea and/or ocular symptoms) in the absence of infection with evidence of aeroallergen sensitisation.

2.3. Assessment of potential confounding factors

We also collected data on other environmental factors that could confound or influence the relationship between fish oil, allergic disease and neurodevelopment. Most of these data were collected retrospectively using specifically designed questionnaires and included information about the pregnancy and birth (anthropometric data, pregnancy/birth complications, gestation), other clinical diseases and common exposures (vaccination, infection, days of day care attendance, length of breastfeeding and medication use including antibiotics), the home environment (including carpeting, siblings, pets, language spoken), and socio-economic factors (maternal and paternal highest year of education, drug and alcohol use, annual income after tax). The Depression Anxiety Stress Scales (DASS-42) [37] was used to measure maternal stress during pregnancy, and at 6 and 18 months post-partum.

2.4. Language assessments

Macarthur-Bates Communicative Development Inventories (Words & Gestures) (MCDI) [38] (see below) were provided to the parents of the infants to complete prior to the 12 month clinical visit for allergy and at the 18 month Neurodevelopmental assessment (see below).

2.5. Neurodevelopmental assessments

Participants were invited to attend a neurodevelopmental appointment at 18 months of age. The assessments were completed by two assessors (Rater 1: n = 50, Rater 2: n = 239) trained in administration of the tests. Three assessments were completed: i) The Bayley Scales of Infant Toddler Development (3rd Edition) (BSID-III) [39] is an internationally recognised clinician-administered tool designed to assess the development in very young children (1–42 months). It consists of 3 scales used to diagnose developmental delay: mental scale for cognitive development, language and personal social development; motor scale for fine and gross motor skills; and behavioural development. Standard scores above 7 are considered within the normal range. And ii) the Achenbach Child Behaviour Checklist (CBCL) [40] was used to assess mental health and behavioural development. It measures parental perceptions of child competencies and behaviours in children aged 18 months to five years. Scales include Affective Problems, Anxiety Problems, Attention Deficit/Hyperactivity Problems, Oppositional Defiant Problems and Pervasive Developmental