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Atopic dysfunction and risk of central nervous system tumours in children

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ARTICLE INFO

Article history:
Received 19 July 2007
Received in revised
form 20 September 2007
Accepted 9 October 2007
Available online 26 November 2007

Keywords:
Childhood cancer
Paediatric cancer
CNS tumours
Brain tumours
Atopy
UKCCS

ABSTRACT

Risk factors for central nervous system (CNS) tumours in children remain largely unknown. Evidence of an inverse relationship between atopy and tumour development exists in adults but little is known about childhood tumours. This study aims to examine the risk of childhood CNS tumours given a history of eczema and asthma.

Cases of children diagnosed with CNS tumours ($n = 575$) and controls ($n = 6292$) from the UK Childhood Cancer Study (UKCCS) were analysed using conditional logistic regression comparing reported histories of allergic disease.

Asthma was statistically significantly and negatively associated with all CNS tumours (odds ratios, OR 0.75, confidence of interval, $CI_{95\%}$: 0.58–0.97), though this was not observed for eczema (OR 0.94, $CI_{95\%}$: 0.74–1.18). Individuals who had suffered both asthma and eczema showed the most significant reduction in risk (OR 0.48, $CI_{95\%}$: 0.28–0.81). Analysis by tumour subtype showed the strongest effect for the medulloblastoma/PNET group.

These results may have a biological explanation with raised immunosurveillance in atopic individuals protecting against the development of brain tumours. Alternative explanations might include bias, reverse causality or confounding.

1. Introduction

Central nervous system (CNS) tumours comprise approximately 20% of all childhood cancers in Europe[1], making them the second most common group of childhood malignancies after leukaemia. Pathology of childhood CNS tumours is distinct from those of adults[2]. Attempts to identify underlying environmental risk factors have largely been unsuccessful with only ionising radiation known to confer an increased risk[3]. Rare genetic disorders such as neurofibromatosis I, Turcot's syndrome and Gorlin's syndrome can also predispose children to CNS tumours, but have been observed in less than 5% of cases[4,5].

Atopy is allergic hypersensitivity stemming from the overproduction of IgE antibodies, typically associated with a Th2 response against common environmental allergens, resulting from an imbalance between the Th1 and the Th2 driven immune responses[6]. Atopy has a complex genetic component [7] and is also influenced by environmental exposures[8].

Atopic individuals are at increased risk of allergic diseases such as asthma, eczema and allergic rhinitis (hay fever), any or all of which can be indicators of atopic dysfunction. The

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2007.10.007

prevalence of asthma [9], eczema and allergic rhinitis[10] has increased in developed countries in recent years, with the UK consistently found to have among the highest levels worldwide[9–11]. The reasons behind this relatively recent trend are not fully understood, though the hygiene hypothesis has some support[12]. This proposes that lower levels of microbial and viral exposure early in life are responsible for the increase in prevalence of allergic disease.

Possible links between atopy and cancer have been widely investigated [13]. Consistent negative associations have been observed with adult brain tumours[14–20]. Decreased risk of neuroblastoma in children has also been associated with atopy, although results did not attain significance[21]. However, there is a lack of published studies addressing the issue of atopy and the risk of childhood CNS tumours, the present study seeks to address this by utilising data from the UK Childhood Cancer Study (UKCCS).

2. Patients and methods

The UKCCS is a population-based case–control study set up with the aim of identifying risk factors for childhood cancer. Full details are described elsewhere[22]. Briefly, UK children diagnosed with cancer before 15 years of age were eligible for the study, which recruited subjects from 1991 to 1994 in Scotland and 1992–1996 in England and Wales. Following histopathological review CNS tumours were categorised into subgroups according to ICD-O morphology codes[22]; details are in Table 1.

Two controls were selected at random for each case from health authorities (England and Wales) or health boards (Scotland), individually matched by birth month/year and region. Non-participating controls were replaced until 2 controls were interviewed. A discussion of deprivation and participation in the study is provided by Law and colleagues[23].

Data were collected from personal interviews of mothers using the same *pro forma* for cases and controls. Mothers reported the history of their child's allergic disease as part of a questionnaire including medical history of the index child, maternal obstetric history, and social contact history.

The following definitions of allergic disease were used as explanatory variables:

(1) *Asthma*: The first version of the questionnaire (January 1992) included a single question on asthma 'Has (*name*) ever had asthma/wheezy bronchitis?' and no questions regarding eczema.The revised (January 1993) questionnaire incorporated a new section on allergic disease replacing the single asthma question. This included 'Has your child *ever* had asthma?' the response to this question in addition to the response to the single question in the first questionnaire provided the indicator variable for asthma in our analysis.

(2) *Wheezing:* The revised questionnaire also introduced detailed questions on wheezing: 'Has your child *ever* had wheezing or whistling in the chest at any time?' with further questions regarding the detail of wheezing if a positive answer was given. This question was asked alongside the asthma question discussed above. Responses were combined and categorised into three groups according to wheeze severity: none, mild/moderate and severe. Individuals were assigned a numerical score based on answers given to the additional questions if parents reported wheezing or whistling in the chest. Children reported by their mothers to have wheezed (yes/no) were given an initial score of 1, and scores were added as follows; the number of attacks suffered in the 12 months following wheeze onset (0 = 0, 1–3 = 1, 4+ = 2) and whether or not the individual had ever suffered limitation of speech or sleep disturbance (both no = 0, yes = 1). The final range of scores was therefore 0–5. Approximately, one-third of individuals reported to have wheezed had scores of 4 or 5 (485/1463 controls and 33/94 cases),

Table 1 – Distribution of CNS tumour subgroups by age and sex

	Diagnosis age (years)		Sex (⩾2 years only)		% of tumours in study
	<2	⩾2	Male (%)	Female (%)	
Controls	1306	6292	3566 (56.7)	2726 (43.3)	–
All CNS tumours	108	575	287 (49.9)	288 (50.1)	100
Glioma	39	326	150 (46.0)	176 (54.0)	56.7
Pilocytic astrocytoma[a]	18	150	69 (46.0)	81 (54.0)	26.1
Medulloblastoma/PNET[b]	31	132	76 (57.6)	56 (42.4)	23.0
Epyndymoma	17	52	29 (55.8)	23 (44.2)	9.0
Other CNS tumours	21	65	32 (49.2)	33 (50.8)	11.3

ICD-O morphology (M) codes for subgroups

Glioma	9380-1, 9400-60, 9382, 9384, 9841
Pilocytic astrocytoma	9421/3
Medulloblastoma/PNET	9470-80
Epyndymoma	9383, 9390-4
Other CNS tumours	Other morphology not listed above in topography C70–C72 (excluding germ cell tumours)

Central nervous system tumours are represented in the topography codes C70–C72.
a Subgroup of glioma.
b Primitive neuroectodermal tumours.