

Mixed handedness prevails among children and adolescents with infantile asthma and diabetes

Preti A, Lai A, Serra M, Zurrida GG. Mixed handedness prevails among children and adolescents with infantile asthma and diabetes. *Pediatr Allergy Immunol* 2008.

© 2008 The Authors

Journal compilation © 2008 Blackwell Munksgaard

Non-right handedness has been associated with allergic diseases and asthma. Infantile diabetes, too, has been associated with non-right handedness but, to date, data are more consistent on a link between left handedness and asthma than on diabetes. We surmised that mixed handedness, as an indicator of neurodevelopmental disturbance of brain laterality, rather than left handedness is more prevalent among children with asthma and diabetes mellitus. A total of 100 families with a child or an adolescent diagnosed with infantile asthma ($n = 50$) or diabetes mellitus type 1 ($n = 50$) attending the Paediatric Clinic of the 'Brotzu' Hospital in Cagliari (Italy) in 2006 agreed to participate in the study. The Annett Hand Preference Questionnaire was used to test handedness. Compared with 99 same-age and -sex controls, cases were marginally less likely to be right handed (71% vs. 86%; OR = 0.82, 95% CI = 0.54–1.25), and statistically more likely to be mixed handed (20% vs. 6%; OR = 3.30, 95% CI = 1.27–8.56) than controls: $\chi^2 = 8.84$, d.f. = 2, $p = 0.01$. Children with asthma or diabetes did not differ from controls by season of birth; however, mixed-handed ($n = 12$, 46%) and left-handed ($n = 6$, 35%) children were statistically more likely to be born in winter as against the other seasons than those who were right handed ($n = 36$, 23%). Severity was also marginally related to the chance of being classified as non-right handed. People with a genetic predisposition to immune disorders could be more likely to have been negatively affected by infection and inflammation during fetal life, thus developing a deviation in handedness during neurodevelopment, as well as suffering the consequence of disordered immunity during childhood, such as allergic reactions (asthma) and immune-mediated damage to specific internal organs (diabetes type 1).

**Antonio Preti^{1,2}, Alessandra Lai¹,
Marianna Serra¹ and Giampiero
Giorgio Zurrida³**

¹Department of Psychology, University of Cagliari, Cagliari, ²Genneruxi Medical Center, Cagliari, ³Azienda Ospedaliera "Brotzu", Paediatric Clinic, Cagliari, Italy

Key words: asthma; left handedness; neurodevelopment; childhood

Dr Antonio Preti, Centro Medico Genneruxi, via Costantinopoli 42, I-09129 Cagliari, Italy
Tel.: +39 070 480922
Fax: +39 070 480922
E-mail: apreti@tin.it

Accepted 4 December 2007

Non-right handedness has been associated with allergic diseases and asthma (1, 2). Abnormal immunity on a neurodevelopmental basis was hypothesized to be involved in these links (1, 3, 4). Among patients with infantile asthma, those with non-right handedness seem subject to a longer course of the disease, with a higher likelihood for symptoms to persist after 18 yr

of age (5). The investigation of the mechanisms behind the higher frequency of non-right handedness in allergic diseases might have, therefore, a prognostic value by itself, besides immediate etiological implications.

Infantile diabetes, too, has been associated with non-right handedness but, to date, data are more consistent on a link between left handed-

ness and asthma than on diabetes (6). An immune-mediated variant of diabetes, which causes destruction of the islet beta cells of the pancreas, is thought to represent a consistent fraction of diabetes with infantile onset (7). Therefore, in infantile diabetes type 1, too, abnormal immunity on a neurodevelopmental basis could account for the higher prevalence of non-right handedness among the affected children. Inconsistency in past investigations could depend on the resorting to an unfit definition of handedness (8). Simply measuring the degree of left-hand use, indeed, might not suffice to distinguish true left-hand users from mixed-hand users, the latter being probably more likely to suffer from a neurodevelopmental disturbance of brain laterality resulting in the wrong control of immunity, which is thought to be at the basis of allergic reactions.

According to Annett, a genetic balanced polymorphism with heterozygote advantage would rule the distribution of hand preference, influenced by a gene for left hemisphere advantage (9). Nevertheless, the resulting right shift in hand skills would also imply random accidents of development affecting individuals by chance, as evidenced by studies on twins showing monozygotic twins with opposite handedness: the mixed handed, more than the left handed, would be the results of accidental events affecting growth in uterus.

We undertook this study to investigate the links between asthma, and diabetes type 1 on the one hand, and hand preference on the other, as an index of brain lateralization, taking into account the hypothesis that mixed handedness, as an indicator of neurodevelopmental disturbance of brain laterality, rather than left handedness is more prevalent among children with asthma and diabetes mellitus. The month of birth was taken as an indicator of the risk of neurodevelopmental insult, as there is some evidence that those who were born in the winter months (December–February) have an enhanced risk of obstetric complications, mainly on an infective basis (10).

Materials and methods

A total of 115 families with a child or an adolescent diagnosed with infantile asthma ($n = 61$) or diabetes mellitus type 1 ($n = 54$) attending the Paediatric Clinic of the 'Brotzu' Hospital in Cagliari (Italy) from January to April 2006 were invited to participate in the study. The parents were asked to allow their children to be tested on a questionnaire inquiring about hand preference when performing some daily actions.

Informed consent was obtained after a brief explanation of the nature and the aims of the study. A total of 15 families declined the invitation. The other 100 agreed to have their children investigated with the questionnaire. Diagnosis was confirmed by a clinician who knew the child/adolescent. Sex was recorded by direct inspection; additional information (age and month of birth) was provided by the parents.

For each index case, a healthy child/adolescent was matched for age and sex, and chosen from those belonging to families attending the same hospital for any reason. A total of 122 families were contacted, 23 families declined the invitation. The healthy status of controls was testified by an experienced paediatrician, who visited the child/adolescent on site. The necessary ethical approval was obtained from the institute's ethics board prior to the commencement of this study.

Procedure

The Annett Hand Preference Questionnaire (HPQ) is a questionnaire designed to elicit hand preference in a list of 12 major actions, six that can be done with a single hand (primary actions), and six that require the use of both hands, with one hand doing the main part of the action (non-primary actions) (11). Subjects are asked if they preferably use the right or the left hand, or either for the following actions: writing, throwing, wielding a racket, striking a match, hammering and brushing their teeth (primary actions); using scissors, threading a needle, sweeping with a broom, using a shovel, dealing cards and opening a jar (non-primary actions). A total laterality score is obtained by summing up all left-hand replies on the queries (0–12), and it is intended to measure a shift from dextrality of the subject according to Annett's shift theory of genetic balanced polymorphism for cerebral dominance (9). Moreover, subjects were assigned to one of three major groups: fully dextral or right handed (D), when subjects reported a preference for the right hand in doing the six primary actions; fully sinistral or left handed (S), when subjects reported a preference for the left hand in doing the six primary actions; ambidextral or mixed handed (M) when subjects were inconsistent in reporting a preference for one specific hand when doing the six primary actions, i.e. they reported a preference for one hand in some of the six primary actions, and for the other hand in the other actions. The scale had been consistently used and tested for reliability and theoretical validity, and it is one of the most commonly used and highly respected inventories to investigate handedness (9).

All questionnaires were completed in the presence of the examiner. To make sure that subjects marked the correct type of hand use, all participants were invited to mimic the six primary actions using toy objects. Children younger than 10 yr of age were checked for consistency in indicating the right and the left hand by inviting them to indicate, on a tablet, what side the right and the left were. No inconsistency was found. In the sample, reliability of the HPQ measured by Cronbach's α was 0.94 among cases and 0.90 among controls.

All data were coded and analyzed using the Statistical Package for Social Sciences (SPSS for Windows 11.0; SPSS Inc, Chicago, Ill, USA). All tests were two-tailed, with $\alpha = 0.05$ because of the explorative nature of the statistical analyses.

Results

The final sample included 50 children with asthma, 50 children with diabetes mellitus type 1, and 99 controls (79 were healthy, 20 children had some kind of heart disease for which the examining pediatrician excluded any immuno-allergic cause). There were no differences by sex and age in the sample between cases and controls (Table 1). Severity of asthma or diabetes was estimated to be mild for 66 children, medium for 30 children and severe for four children.

Among children with asthma, 34 subjects (68%) were classified on the HPQ as right handed, 11 (22%) were classified as mixed handed and five (10%) were classified as left handed; among children with diabetes, 37 sub-

jects (74%) were classified as right handed, nine (18%) as mixed handed and four (8.0%) as left handed. Among controls, 85 subjects (86%) were classified as right handed, six (6%) as mixed handed and eight (8%) as left handed.

This classification was corroborated by the distribution of the scores on the HPQ, with the left handed scoring statistically higher than the right handed and the mixed handed, both among cases (ANOVA, $F = 286.44$, d.f. = 2/97, $p = 0.0001$, Bonferroni's $p < 0.001$ in all comparisons) and among controls (ANOVA, $F = 227.77$, d.f. = 2/96, $p = 0.0001$, Bonferroni's $p < 0.001$).

Cases were marginally less likely to be right handed (71% vs. 86%; OR = 0.82, 95% CI = 0.54–1.25), and statistically more likely to be mixed handed (20% vs. 6%; OR = 3.30, 95% CI = 1.27–8.56) than controls: $\chi^2 = 8.84$, d.f. = 2, $p = 0.01$. The difference held even when the sample was split by diagnosis: cases with asthma were statistically more likely to be mixed handed than controls (OR = 3.63, 95% CI = 1.26–10.39) and the same emerged from the cases affected by diabetes (OR = 2.97, 95% CI = 1.00–8.81).

Severity was marginally related to the chance of being classified as non-right handed: children with medium to severe illness were more likely to be non-right handed ($n = 14$, 41%) than those with a mild degree of the illness ($n = 15$, 22%): $\chi^2 = 3.71$, d.f. = 1, $p = 0.054$.

Children with asthma or diabetes did not differ from controls by season of birth; however, mixed-handed ($n = 12$, 46%) and left-handed ($n = 6$, 35%) children were statistically more likely to be born in winter as against the other seasons than those who were right handed ($n = 36$, 23%): Kruskal–Wallis test (born in winter as against born in any other season, by handedness), $\chi^2 = 6.59$, d.f. = 2, $p = 0.037$ (Table 2).

Discussion

The results of this study corroborate past investigations claiming a link between non-right handedness and asthma, and extend the finding to children with diabetes type 1. Mixed handedness, more than left handedness, seems to be a feature of asthma and infantile diabetes: in past

Table 1. Characteristics of the sample

	Cases, n = 100	Controls, n = 99
Sex		
Males (%)	58 (58)	53 (53)
Females (%)	42 (42)	46 (47)
Age		
Mean (s.d.)	10.4 (3.1)	10.8 (3.3)
Median	10.0	10.0
Mode	10.0	9.0
Handedness		
Right handed (%)	71 (71)	85 (86)
Mixed handed (%)	20 (20)	6 (6)
Left handed (%)	9 (9)	8 (8)
Annett's HPQ scores, mean (s.d.)		
Right handed	0.1 (0.4)	0.4 (0.9)
Mixed handed	4.4 (2.6)	3.0 (1.6)
Left handed	10.4 (1.8)	8.8 (2.1)
Season of birth		
Winter (Dec, Jan, Feb) (%)	26 (26)	28 (28)
Spring (Mar, Apr, May) (%)	18 (18)	23 (23)
Summer (Jun, Jul, Aug) (%)	26 (26)	28 (28)
Autumn (Sep, Oct, Nov) (%)	30 (30)	20 (20)

Table 2. Distribution of season of birth by handedness, all samples (n = 199)

	Winter	Spring	Summer	Fall	Total
Right handed (%)	36 (23.1)	34 (21.8)	44 (28.2)	42 (26.9)	156 (78.3)
Mixed handed (%)	12 (46.2)	3 (11.5)	7 (26.9)	4 (15.4)	26 (13.0)
Left handed (%)	6 (35.3)	4 (23.5)	3 (17.6)	4 (23.5)	17 (8.5)

investigations, mixed handedness was found to prevail among children with both asthma and allergic rhinitis, who were more likely to be affected by disordered immunity (2). In our sample, children with a medium to severe course of their illness were marginally more likely to be classified as non-right handed, a finding consistent with past reports indicating that children with infantile asthma who were non-right handed were also subject to a longer, putatively more severe course of the disease (5).

Altered neurodevelopment is thought to contribute to the fixation of mixed handedness (3, 9), whereas fully right handedness and left handedness would develop according to some, still unfound gene(s) implied in brain lateralization (9). Obstetric insults are involved in the development of non-right handedness, including perinatal adverse events with an infective basis (12). Altered immunity on a constitutional (hence, genetic) basis could contribute to the risk of perinatal insults, which are thought to involve an enhanced risk of neurodevelopmental disorders (10). In our study, children who were classified as non-right handed were more likely to be born in the winter months than in any other season: winter months are thought to be associated with an enhanced risk of obstetric adverse events, particularly with an infective basis.

The complexity of the interplay between the nervous system and the immune system makes it impossible to figure out the mechanism responsible for the interactions between handedness and immune system in these patients. We can speculate that people with a genetic predisposition to immune disorders might be more likely to be negatively affected by infection and inflammation during fetal life, thus developing a deviation in handedness during neurodevelopment, as well as suffering the consequence of disordered immunity during childhood in the form of allergic reactions and immune-mediated damage to specific internal organs, as for example the destruction of the islet beta cells of the pancreas thought to be the cause of diabetes type 1 (7).

More complex interactions between immunity and lateralization have been suggested, with neurodevelopmental insult leading to deviations in brain lateralization which, in turn, would produce abnormalities in the immune response, these latter leading to infantile disorders such as asthma and diabetes type 1 (2, 5). Animal experiments proved that alterations in brain laterality are associated with changes in lymphocyte functions (13). In humans, higher levels of right-prefrontal electroencephalographic activation predict poorer immune response (14).

Larger samples, allowing a wider distinction of subtypes in the investigated illnesses concurrently with a reliable survey of their obstetric history, would contribute to exploring these hypotheses better. Testing handedness in children with asthma, however, would be a useful addendum to identify children with a potentially longer and more severe course of the disorder, although on the basis of current knowledge it can be foreseen that this would probably have a minor prognostic value for the risk of the disease.

Acknowledgments

The authors wish to thank all the families who agreed to participate in this study, the paediatricians who provided their help in assessing the participants, and Ms Daniela Bergallo and Ms Vittoria Rubino for her help in revising the English version. Research was supported by internal funds only, and no conflict of interest is foreseeable.

References

- COREN S. Handedness and allergic response. *Int J Neurosci* 1994; 76: 231–6.
- KROMMYDAS G, GOURGOULIANIS KI, ANDREOU G, MOLYVDAS PA. Left-handedness in asthmatic children. *Pediatr Allergy Immunol* 2003; 14: 234–7.
- GESCHWIND N, BEHAN P. Left-handedness: association with immune disease, migraine, and developmental learning disorder. *Proc Natl Acad Sci USA* 1982; 79: 5097–100.
- WEINSTEIN RE, PIEPER DR. Altered cerebral dominance in an atopic population. *Brain Behav Immun* 1988; 2: 235–41.
- KROMMYDAS G, GOURGOULIANIS KI, RAFTOPOULOS V, et al. Non-right handedness and asthma. *Allergy* 2004; 58: 892–3.
- SEARLEMAN A, FUGAGLI AK. Suspected autoimmune disorders and left-handedness: evidence from individuals with diabetes. Crohn's disease and ulcerative colitis. *Neuropsychologia* 1987; 25: 367–74.
- DEVENDRA D, LIU E, EISENBARTH GS. Type 1 diabetes: recent developments. *BMJ* 2004; 328: 750–4.
- MORFIT NS, WEEKES NY. Handedness and immune function. *Brain Cogn* 2001; 46: 209–13.
- ANNETT M. The right shift theory of a genetic balanced polymorphism for cerebral dominance and cognitive processing. *Curr Psychol Cogn* 1995; 14: 1–54.
- YOLKEN RH, TORREY EF. Viruses, schizophrenia, and bipolar disorder. *Clin Microbiol Rev* 1995; 8: 131–45.
- ANNETT M. A classification of hand preference by association analysis. *Br J Psychol* 1970; 61: 303–21.
- RAMADHANI MK, KOOMEN I, GROBBEE DE, VAN DONSELAAR CA, MARCELINE VAN FURTH A, UITERWAAL CS. Increased occurrence of left-handedness after severe childhood bacterial meningitis: support for the pathological left-handedness hypothesis. *Neuropsychologia* 2006; 44: 2526–32.
- NEVEU PJ. Asymmetrical brain modulation of the immune response. *Brain Res Rev* 1992; 17: 101–7.
- ROSENKRANZ MA, JACKSON DC, DALTON KM, et al. Affective style and in vivo immune response: neuro-behavioral mechanisms. *Proc Natl Acad Sci USA* 2003; 100: 11148–52.