The relationship between allergic diseases and internalising and externalising behaviours in Spanish children: A cross-sectional study

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Abstract

Introduction and objectives: The relationship between allergic diseases and behavioural disorders is still unclear. The objective of this study was to describe and compare children's behaviour (internalising and externalising) across a sample of children aged 6-11 years with and without allergic diseases. Materials and methods: This was a cross-sectional observational case-control study. A survey to 366 families (194 allergic cases and 172 controls), including a child behaviour checklist (CBCL) and a socio-demographic questionnaire with questions related to family, school education, health conditions and allergy symptoms, was administered. Results: Children with a diagnosis of allergy showed higher scores in the overall CBCL score (standardised mean differences [SMD]=0.47; confidence intervals [CI]: 0.26-0.68) and in the internalising and externalising factors (SMD=0.52 and SMD=0.36, respectively) than non-allergic children. Odds ratio (OR) analyses showed a higher risk (OR=2.76; 95% CI [1.61 to 4.72]) of developing a behavioural difficulty in children diagnosed with allergies. Age and level of asthma appear as modulatory variables. Conclusions: Children aged 6-11 years diagnosed with allergies showed larger behavioural problems than non-allergic children, especially in the case of internalising behaviours. These findings suggest the importance of attending to them and treating them in the early stages of diagnosis to avoid future psychological disorders.

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Introduction

The prevalence of allergic diseases has increased globally for more than 50 years, especially in industrialised countries and in children aged less than 18 years. This rise in the prevalence of allergies has a great impact on societies as it generates high healthcare costs. Families and children with allergic diseases are particularly affected and bear the maximum burden, which is reflected in reduction of their quality of life, an increased risk of psychological disorders and numerous medical and non-medical comorbidities.

Over the past few decades, evidence about the relationship between common allergies (related to environmental factors, foods and drugs, their main symptoms (such as asthma, allergic rhinitis [AR] or atopic dermatitis [AD]) and mental health problems in children and young adults has become stronger. Asthma is related with a higher risk of internalising disorders (such as anxiety and depression), externalising disorders (such as oppositional defiant or disruptive behaviour disorders) or poorer social and mental well-being. Different studies on allergic rhinitis in children and pre-schoolers have shown a relationship between internalising and sleep problem behaviours. In addition, atopic dermatitis has been associated in different studies with several mental comorbidities such as attention deficit disorder, anxiety and depression. However, a recent meta-analysis of 35 studies on atopic dermatitis has found opposite results.

On the other hand, the relation between allergic diseases and these internalising/externalising difficulties is not clear. Some psychological approaches have suggested that children could have psychological adjustment difficulties because of an allergy and its symptoms, or that these could be influenced by intra-familial or socio-emotional factors related to family circumstances. Others have explored the relationship with an underlying biological process related to the serotoninergic system.

In spite of these evidences, there is a lack of studies assessing outcomes with well-validated instruments that compare a clinical allergic sample with a similar control sample of non-allergic children. In addition, no study has assessed the possible relationship between multiple comorbid allergies and behavioural problems.

The aim of this study was to assess relationship between allergic diseases and behavioural problems (internalising and externalising). The possible influence of intra-familial conditions (such as level of stress in the family, affective expressions, resilience and parental authority) into the origin of behavioural problems in allergic children was also studied. In addition, we aimed to assess the relationship between the severity of allergy (mild or moderate asthma and the number of allergic comorbidities) and the degree of behavioural problems.

Methods

Hypothesis and design

The principal hypothesis of this study was that children (aged 6 to 11 years) with a diagnosis of an allergic disease would show higher behavioural problems (internalising and externalising problems), assessed using the child behaviour checklist (CBCL), than the children without a diagnosis of allergic disease.

The secondary hypothesis was that children (aged 6 to 11 years) with a diagnosis of an allergic disease would show higher scores on eight syndrome subscales of the CBCL scale (anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour and aggressive behaviour) than children without a diagnosis of allergic disease.

Third hypothesis was that there is a positive relation between the severity of the allergy (assessed by the degree of asthma and the number of allergic comorbidities) and the level of behavioural problems.

This study design was carried out as a multicentre, case-control, cross-sectional study.

Sample

The study population included two groups. The first group (cases/patients) comprised families with a child diagnosed with an allergic disease. To be eligible to be included in this group, families had to fulfil the following criteria: (i) they must have a male or female child (aged 6 to 11 years), (ii) being treated in an external paediatric pneumology/allergology service, (iii) for a clinically diagnosed mild or moderate environmental allergy (including pollen, mould, dust or pets), food allergy, medication allergy, allergic asthma, allergic rhinitis or atopic dermatitis, and (iv) allergy symptomatology must be stable and well controlled by a clinician. Exclusion criteria included: (i) children with a severe clinical diagnosis of allergy, (ii) comorbidity of another primary pathology, (iii) having a direct family member (parent or siblings) with severe mental disorder (Diagnostic and Statistical Manual of Mental Disorders, 5th version [DSM-V] criteria), and (iv) being hospitalised. The sample for this group was recruited from the Clinical Hospital of San Carlos, located in Madrid (Spain). A clinician individually informed families about the study and its purposes and asked them about their interest to participate in the study.

The second group (controls) comprised families with healthy children. To be included in this group, families must fulfil the following criteria: (i) they must have a male or female child (aged 6 to 11 years). Exclusion criteria for this group included having a child: (i) with a clinical diagnosis of allergy, (ii) comorbidity of another primary pathology, (iii) direct family (parents or siblings) with a severe mental disorder (DSM-V criteria), and (iv) being hospitalised. The full sample for this group was recruited from a state-financed school in Madrid (Spain). In this case, the team met the families of the children to inform them about the study and its purposes. Forms (informed consent and survey forms) were sent by post at their homes. Families interested to participate in the study forwarded the documentation with the requested information.

Parents of both groups signed the written informed consent before included in the study. Study approval was obtained from the Ethical and Scientific Research Committee of the San Carlos Clinic Hospital, Madrid (Spain) in April 2019 (internal code: 19/108-E).
Assessment

Socio-demographic and emotional climate in the family

To collect socio-demographic information, the team developed an ad hoc questionnaire with questions related to age, sex, number of brothers and sisters of the child and family structure (nuclear, separated, adoptive etc.). To detect emotional circumstances of the family, a brief ad hoc questionnaire was used. In this questionnaire, parents used a 3-point Likert scale (low, medium or high) to rate their perceived levels of stress in the family, affective expressions, resilience to cope with familial problems and difficulties, and their authority or effectiveness in establishing rules in the family (see Supplementary material: ‘Data of Your Child’s Family Context’).

Allergy information

Information about the allergy of the participants of allergic group was collected directly by a clinician from medical files. It includes information concerning allergen (pollen, mould, dust, pets, food or medication), level of asthma (mild or moderate), atopic dermatitis, allergic rhinitis and food intolerance. Participants in the control group were also asked all these questions in order to ensure that they did not suffer from any allergy or show symptoms of allergy.

Behavioural outcome measure

To assess behavioural problems, parents completed the child behaviour checklist (CBCL). The CBCL can be applied to subjects aged 4-16 years. It includes 113 statements recorded on a 4-point (0-3) Likert scale (0 = ‘false or rarely’; 3 = ‘true or very often’). The items are grouped into nine independent factors: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, attention problems, rule-breaking behaviour, aggressive behaviour and other problems. The scale gives three summary scores related to internalising behaviour problems (formed by the sum of the factors of anxious/depressed, withdrawn/depressed and somatic complaints), externalising behaviour problems (sum of rule-breaking behaviour and aggressive behaviour) and a total score (obtained by the addition of all the factors). To interpret these scores, direct scores were converted to a T scale where scores between 65 and 70 were considered as critical borderline clinical range. Higher scores meant higher levels of behavioural problems, rule-breaking behaviour, aggressive behaviour and other problems. The scale gives three summary scores related to internalising behaviour problems (formed by the sum of the factors of anxious/depressed, withdrawn/depressed and somatic complaints), externalising behaviour problems (sum of rule-breaking behaviour and aggressive behaviour) and a total score (obtained by the addition of all the factors). To interpret these scores, direct scores were converted to a T scale where scores between 65 and 70 were considered as critical borderline clinical range. Higher scores meant higher levels of behavioural problems. We used the Spanish version of the CBCL for children aged 6-18 years.

Parents completed the parent rating scale of the CBCL and the ad hoc questionnaires.

Sample size calculation

Taking into account that the 10% of general child population can show any disruptive behaviour, and accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 195 subjects were necessary in both groups in order to find a statistically significant difference in proportions, expected to be 0.1 in allergic group and 0.2 in the control group.

Statistical analysis

Sample description was reported by mean values and standard deviations (SDs) for continuous variables, whereas frequencies and percentages described categorical variables.

To contrast the main hypothesis of the study we used simple means of comparisons (Student’s t-test or the Mann-Whitney U test). In addition, simple mean differences and standardised mean differences (SMD) with 95% confidence intervals (95% CI) and odds ratios (ORs) were determined. SMD could be easily interpreted following the rule of thumb: scores from 0 to 0.2 indicated a small effect, values near to 0.5 suggested medium effect, and 0.8 or above values could be interpreted as a large effect. To calculate OR we separated the obtained CBCL scores using a T score of 65 as the cut-off point, marked by the original authors of the scale as ‘clinical range’. An OR value of more than 1 was interpreted as higher odds of the described event occurring, given the particular exposure. In case of any statistically significant differences in socio-demographic or familial variables between groups, secondary analysis was performed by logistic regression, adjusting for covariates.

Association between the severity of allergy (assessed by the degree of asthma and the number of allergic comorbidities) and the level of behavioural problems was examined using a Student’s t-test (degree of asthma has only two categories) and a Pearson correlation (one participant could have from one to four allergies). For these dose-rela- tion analyses, we used the allergic group.

An independent and blinded statistician performed analyses using SPSS V.21 (IBM SPSS Statistics for MAC, version 24.0, IBM Corp., Armonk, NY) and Jamovi 1.2 (Jamovi project, Jamovi, version 1.2).

Results

Sample description

A total of 456 families were assessed for eligibility; twenty-three (5.04%) did not meet the selection criteria and 67 refused to participate (14.69%). Finally, we recruited a total of 366 families (80.26%) (194 patients and 172 controls) from May to July 2019. Table 1 presents characteristics of the main sample obtained from the questionnaires distributed in groups.

The total sample had a mean age of 8.68 years, while the allergic group showed a higher mean age than the control group. Overall, allergic group reported allergies to environmental elements (pollen, mould, dust or pets); 38 children indicated food allergies and only five showed allergy to pharmacological compounds. All patients in the allergic group were diagnosed with asthma, and 123 children had atopic dermatitis. The most frequent family structure was traditional or nuclear followed by separated or divorced. Assessment of emotional circumstances from the context of family indicated that the level of stress was
predominately low, with a high degree of affective expressions and medium degree of resilience and authority. No significant differences were observed between allergic and control groups in relation to intra-familial conditions.

**Comparisons of behaviour (CBCL) by group (allergic and control groups)**

Table 2 shows scores on the CBCL scale. The overall sample obtained a mean total score of 26.71, indicating non-clinical behaviour. Allergic children showed higher scores, with a significant mean difference of 10.27 points above the control group (SMD = 0.47; 95% CI [0.26 to 0.68]). Internalising and externalising subscales reported similar differences between groups with medium effect sizes (SMD = 0.52; 95% CI [0.32 to 0.73] and SMD = 0.36; 95% CI [0.15 to 0.56], respectively).

The remaining factors, except ‘rule-breaking behaviour’, showed similar statistical results (P > 0.025) with medium effect sizes. The largest differences were detected in the subscales of ‘somatic complaints’ (SMD = 0.57) and ‘thought problems’ (SMD = 0.43), while the smallest differences were in the subscale of ‘attention problems’ (SMD = 0.29) and ‘others’ (SMD = 0.26).

Logistic regressions adjusted for covariates (age and number of siblings) reported similar results (P < 0.01 for the total score, internalising and externalising subscales; and P < 0.05 for the remaining factors except for the ‘rule-breaking behaviour’ subscale). A comparison between the younger (aged 6–8 years) and the older participants (aged 9–11 years) showed smaller differences (SMD) in all scores, especially for externalising sub-domain (Table 3).
### Table 2 Comparisons of child behaviour checklist (CBCL) scores by groups.

<table>
<thead>
<tr>
<th></th>
<th>Total (N=366)</th>
<th>Allergic (n=194)</th>
<th>Control (n=172)</th>
<th>P-value</th>
<th>Mean difference</th>
<th>SMD (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBCL total, mean (SD)</td>
<td>26.71 (21.32)</td>
<td>31.28 (22.45)</td>
<td>21.55 (18.74)</td>
<td>&lt;0.001</td>
<td>-10.27</td>
<td>0.47 [0.26 to 0.68]</td>
<td>2.76 [1.61 to 4.72]</td>
</tr>
<tr>
<td>Anxious/depressed</td>
<td>3.39 (3.52)</td>
<td>4.06 (3.88)</td>
<td>2.63 (2.9)</td>
<td>&lt;0.001</td>
<td>-1.55</td>
<td>0.41 [0.21 to 0.62]</td>
<td>2.83 [1.41 to 5.66]</td>
</tr>
<tr>
<td>Withdrawn/ depressed</td>
<td>1.63 (2.32)</td>
<td>2 (2.65)</td>
<td>1.21 (1.8)</td>
<td>&lt;0.001</td>
<td>-0.88</td>
<td>0.34 [0.14 to 0.55]</td>
<td>1.5 [0.84 to 2.67]</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>2.33 (2.7)</td>
<td>3.03 (2.98)</td>
<td>1.54 (2.07)</td>
<td>&lt;0.001</td>
<td>-1.49</td>
<td>0.57 [0.36 to 0.78]</td>
<td>1.51 [1.38 to 4.53]</td>
</tr>
<tr>
<td>Social problems</td>
<td>2.45 (2.7)</td>
<td>2.93 (2.89)</td>
<td>1.91 (2.35)</td>
<td>&lt;0.001</td>
<td>-1.08</td>
<td>0.38 [0.18 to 0.59]</td>
<td>3.31 [1.52 to 7.19]</td>
</tr>
<tr>
<td>Thought problems</td>
<td>2.07 (2.53)</td>
<td>2.57 (2.71)</td>
<td>1.5 (2.18)</td>
<td>&lt;0.001</td>
<td>-1.18</td>
<td>0.43 [0.22 to 0.64]</td>
<td>2.41 [1.19 to 4.89]</td>
</tr>
<tr>
<td>Attention problems</td>
<td>4.18 (3.71)</td>
<td>4.69 (3.78)</td>
<td>3.61 (3.55)</td>
<td>0.002</td>
<td>-1.29</td>
<td>0.29 [0.09 to 0.5]</td>
<td>1.44 [0.71 to 2.91]</td>
</tr>
<tr>
<td>Rule-breaking behaviour</td>
<td>1.63 (1.96)</td>
<td>1.74 (2.11)</td>
<td>1.5 (1.76)</td>
<td>0.221</td>
<td>-0.13</td>
<td>0.12 [-0.08 to 0.33]</td>
<td>1.69 [0.72 to 4.91]</td>
</tr>
<tr>
<td>Aggressive behaviour</td>
<td>5.02 (4.61)</td>
<td>5.92 (4.81)</td>
<td>4 (4.16)</td>
<td>&lt;0.001</td>
<td>-1.93</td>
<td>0.42 [0.22 to 0.63]</td>
<td>2.5 [1.17 to 5.36]</td>
</tr>
<tr>
<td>Others</td>
<td>3.97 (2.96)</td>
<td>4.29 (3.02)</td>
<td>3.61 (2.86)</td>
<td>0.025</td>
<td>-0.69</td>
<td>0.26 [0.06 to 0.47]</td>
<td>0.88 [0.47 to 1.57]</td>
</tr>
<tr>
<td>Internalizing</td>
<td>7.36 (7.29)</td>
<td>9.10 (8.14)</td>
<td>5.39 (5.59)</td>
<td>&lt;0.001</td>
<td>-3.93</td>
<td>0.52 [0.32 to 0.73]</td>
<td>2.45 [1.54 to 3.89]</td>
</tr>
<tr>
<td>Externalizing</td>
<td>6.65 (6.14)</td>
<td>7.67 (6.41)</td>
<td>5.50 (5.62)</td>
<td>&lt;0.001</td>
<td>-2.18</td>
<td>0.36 [0.15 to 0.56]</td>
<td>1.77 [1.03 to 3.04]</td>
</tr>
</tbody>
</table>

CBCL: child behaviour checklist; CI: confidence interval; SD: standard deviation; SMD: standardized mean difference; OR: odds ratio.

### Table 3 Comparisons of child behaviour checklist (CBCL) scores by groups and age (under and over 9 years old).

<table>
<thead>
<tr>
<th></th>
<th>Under 9 years</th>
<th>Over 9 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allergic (n=78)</td>
<td>Control (n=95)</td>
</tr>
<tr>
<td>CBCL total, mean (SD)</td>
<td>30.69 (21.53)</td>
<td>19.08 (16.06)</td>
</tr>
<tr>
<td>Anxious/depressed</td>
<td>4.01 (3.88)</td>
<td>2.28 (2.63)</td>
</tr>
<tr>
<td>Withdrawn/ depressed</td>
<td>1.62 (1.96)</td>
<td>1.12 (1.81)</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>3.05 (3.37)</td>
<td>1.38 (1.83)</td>
</tr>
<tr>
<td>Social problems</td>
<td>2.74 (2.66)</td>
<td>1.72 (1.95)</td>
</tr>
<tr>
<td>Thought problems</td>
<td>2.62 (2.63)</td>
<td>1.39 (2.13)</td>
</tr>
<tr>
<td>Attention problems</td>
<td>4.81 (3.86)</td>
<td>3.21 (3.30)</td>
</tr>
<tr>
<td>Rule-breaking behaviour</td>
<td>1.58 (1.83)</td>
<td>1.27 (1.61)</td>
</tr>
<tr>
<td>Aggressive behaviour</td>
<td>5.97 (4.37)</td>
<td>3.36 (3.38)</td>
</tr>
<tr>
<td>Others</td>
<td>4.29 (3.35)</td>
<td>3.36 (2.60)</td>
</tr>
<tr>
<td>Internalizing</td>
<td>8.68 (8.31)</td>
<td>4.78 (5.05)</td>
</tr>
<tr>
<td>Externalizing</td>
<td>7.55 (5.66)</td>
<td>4.63 (4.62)</td>
</tr>
</tbody>
</table>
Odds Ratios

According to the results, children with allergies are 2.76 times more likely to have behavioural problems than children without allergies (P=0.001; 95% CI [1.61 to 4.72]). The OR for externalising and internalising subcales showed significantly similar results (P=0.03 and 0.001, respectively), indicating the same relationship. The OR was higher in internalising factor than in externalising factor (2.45 against 1.77). The factor of 'social problems' obtained the highest OR in the overall scale (OR=3.31; 95% CI [1.52 to 7.19]) followed by the 'anxious/depressed' factor (OR=2.83; 95% CI [1.41 to 5.66]). Factors such as 'withdrawn/depressed', 'attention problems' and 'rule-breaking behaviour' showed the smallest and non-statistically significant OR (95% CI included value of 1).

Allergy severity

Comparisons between children with mild or moderate level of asthma showed higher and significant scores in the subsample of moderate asthma (see Table 4) in the total score and in the internalising sub-domain.

Correlations between the number of allergies and CBCL scores did not show relevant results (P<0.05).

Discussion

The prevalence of allergies in children has grown in last few decades. Allergies are very often associated with physical, mental and emotional problems that could be detected through child's behaviour and feelings.

The results of this study confirm the main hypothesis that children with allergic diseases show a higher risk of suffering with behavioural problems (internalising and externalising) than healthy subjects. Both types of factors show differences, with those in internalising factor appear to be greater. These results are similar to that of other studies.

The secondary hypothesis also appears to be confirmed. Children with allergies showed higher scores in all the subscales with the exception of 'rule-breaking behaviour'.

The fact that the subscale of 'rule-breaking behaviour' did not show significant differences and the absence of differences in the emotional climate of the family (stress, affective expression, resilience or authority) could be related, are in agreement with the results of similar studies that indicated a relationship between oppositional-defiant behaviours and style of parental discipline, socio-environmental factors and personality. However, this point needs further research.

Analysing each subscale, 'somatic complaints' stands out for having the largest mean differences. Obviously, this is directly related to the symptoms derived from allergies (asthmatic, rhinitis and atopic dermatitis). The rest of the subcales could be connected following other similar studies. Children with social, thinking or attention problems experience difficulties in expressing their feelings and emotions; this can produce anxious/depressed symptoms or aggressive behaviours. These two subcales have shown the largest differences in each factor (internalising and externalising, respectively). Secondary analyses comparing scores by group and age have revealed very interesting results that need to be explored in detail. It seems that these differences tend to decrease, as children grow older. Maybe this could be related to the maturation process of child, the acquisition of new behavioural skills, or to the lesser dependency on parents.

Third hypothesis related with dose-relation analyses showed mixed results. While there was a relation between degree of asthma (mild or moderate) and general and internalising behavioural problems, these relations disappear when compared with the number of allergies. This situation may be due to the dispersion of data, and a larger sample size may be required.

In spite of the efforts to control methodological aspects, these results must be considered within the context of some limitations. Firstly, the study's principal limitation is related to its cross-sectional design. It would be desirable to carry out a longitudinal study to increase the internal validity of results. Secondly, despite efforts to recruit subjects in different groups, we failed in the control group, in which the number of participants was less than expected in the sample size calculations. This limitation could be associated with the lack of parental involvement in a study whose results do not concern them. Thirdly, we have used a simple and ad hoc questionnaire to assess some variables (aspects related to allergy and emotional climate in the family). It would be desirable to use a more precise and well-validated tool to asses these aspects and to make comparisons with other similar studies possible. In this context, findings should be interpreted with caution, as it is not possible to ensure that these differences imply a causal phenomenon.

Lastly, in this study OR results indicated that all factors, including the overall CBCL score and each individual factor, showed a higher risk of clinical behavioural problems in the sample of allergic children. In some cases, the risk of showing difficulties or problems is more than three times in the allergic group than in the

Table 4 Comparisons of child behaviour checklist (CBCL) scores by level of asthma (mild or moderate).

<table>
<thead>
<tr>
<th></th>
<th>Mild asthma (n=151)</th>
<th>Moderate asthma (n=43)</th>
<th>P-value</th>
<th>Mean difference</th>
<th>SMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBCL total, mean (SD)</td>
<td>29.3 (21.4)</td>
<td>38.3 (24.8)</td>
<td>0.019</td>
<td>-9.08</td>
<td>0.4 [1.51 to 16.64]</td>
</tr>
<tr>
<td>Internalizing</td>
<td>8.49 (7.68)</td>
<td>11.3 (9.41)</td>
<td>0.049</td>
<td>-2.77</td>
<td>0.34 [0.01 to 5.52]</td>
</tr>
<tr>
<td>Externalizing</td>
<td>7.26 (6.05)</td>
<td>9.12 (7.47)</td>
<td>0.09</td>
<td>-1.85</td>
<td>0.29 [0.32 to 4.03]</td>
</tr>
</tbody>
</table>

CBCL: child behaviour checklist; CI: confidence interval; SD: standard deviation; SMD: standardized mean difference.
control group (social problems). These findings suggest the need to investigate new strategies and interventions to treat and prevent possible mental health diseases in childhood, which is such an important stage in a person’s development.41

Conclusions

These findings suggest an important association between suffering from allergies and the presence of behavioural problems in children aged 6-11 years. This relationship is stronger in internalising behaviours. Age of the children and moderate asthma appear to be protective variables. Because of the importance of children’s proper mental and physical development and their transition to adulthood, clinicians should pay more attention to possible symptoms related to mental health or behavioural problems, especially in children with multiple allergic diseases or comorbidities. Early treatment and prevention programmes with children and families that could avoid or reduce the probability of manifesting these difficulties in successive stages are warranted.

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Ethical disclosures

Protection of human subjects and animals in research: This study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Right to privacy and informed consent: All participants signed the informed consent. The author for correspondence is in possession of this document.

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Declaration of interest

The authors have no conflicts of interest to disclose.

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