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Parental perception of their child's Quality of Life in children with non-Immunoglobulin-E mediated gastrointestinal allergies

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Short title: Quality of life of children with non-IgE-mediated gastrointestinal allergy

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Abstract

Background:

Food allergy can have a significant impact on health related quality of life (HRQoL). Parental proxy questionnaires are commonly used when children are too young to complete questionnaires themselves. Little data is available on HRQoL in children with non-IgE-mediated gastrointestinal food allergy (GIFA). The aim of this study was to evaluate HRQoL in these children by parent proxy.

Methods:

A cross-sectional questionnaire study was conducted with children 2-16 years old with confirmed (GIFA). Parents of these children completed the Paediatric Quality of Life Inventory (PedsQL^{TM}) and the Family Impact module of the PedsQL. The PedsQL scores were compared to two published cohorts: functional abdominal pain (FAP) and IgE-mediated food allergy.

Results:

Fifty-two parents of children with GIFA completed the PedsQL^{TM} parent proxy. The GIFA cohort had significantly better overall HRQoL compared to the FAP cohort, but lower emotional functioning scores. The GIFA cohort also had poorer physical QoL compared to the IgE cohort (all $p<0.05$). The more foods

excluded, comorbidity of nasal congestion, abdominal pain, back arching, the persistence of flatus and gastrointestinal symptom severity after elimination diet were related to poorer QoL in this non-IgE cohort. Regression analyses showed that number of foods and nasal congestion significantly predicted total QoL score as perceived by parents.

Conclusions:

This study has shown that different areas of HRQoL of children with GIFA are affected compared to children with FAP or IgE-mediated food allergy, highlighting the need for a specific GIFA HRQoL questionnaire to better understand the impact on these children.

Background

The impact of ImmunoglobulinE (IgE)-mediated food allergy on children and their families, particularly for health-related quality of life (HRQoL), has been well-documented (1-3). Studies have shown that food allergies can cause significant psychological and emotional burden on children and their families compared to children without food allergy (1, 4). Valentine and Knibb for example showed that children with food allergies had difficulties with school lunches, experienced restrictions on favourite foods and carrying medication had a negative influence on HRQoL (5). Parents reported lower HRQoL with regards to shopping and concern over the health of their child compared to parents of children without food allergy (5).

Specific food allergic HRQoL questionnaires have now been validated for IgE-mediated food allergy. These comprise questions such as food anxiety, social and dietary eliminations and the emotional impact on parents and their children (8-10). There is, however, a paucity of data assessing the impact on children's HRQoL in non-IgE-mediated gastrointestinal food allergies (GIFA) (11, 12). The European Academy of Allergy and Clinical Immunology have acknowledged that a validated tool to measure HRQoL in this group of children is required and the tools available for children with IgE-mediated food allergy are not suitable for those with GIFA (9).

Studies using more generic HRQoL measures have been used. For example, Klinnert *et al* (13) looked at family HRQoL in children diagnosed with eosinophilic oesophagitis, a GIFA condition, using a generic paediatric quality of life questionnaire (PedsQL) and found that these children and their families reported a diminished HRQoL compared to healthy individuals, with lower scores in the children with increased severity of symptoms and number of foods eliminated (13). Meyer *et al* looked at the impact of GIFA on the family (using the Family Impact Module PedsQL^{TM} questionnaire) and showed that this was worse compared to families of children with chronic diseases such as sickle cell disease and intestinal failure (14).

Children with GIFA are usually young and present with symptoms in infancy. Parental proxy questionnaires are commonly used when children are too young to complete questionnaires themselves. The aim of the present study was to better understand the HRQoL of children with GIFA through assessment by parental proxy and comparison with published data on HRQoL of children with IgE-mediated food allergy and children with functional abdominal pain (FAP) (15, 16)

Method

Design

A cross-sectional questionnaire study was carried out at Great Ormond Street Hospital, London, United Kingdom from December 2011 and November 2013. Ethical approval was granted for the study (NR11/LO/1177) and all parents gave written informed consent.

Participants and Procedure

Parents of children aged 2 to 16 years were approached to take part in the study where an elimination diet had improved a child's symptoms of GIFA. This included children with eosinophilic gastrointestinal disorders, allergic dysmotility disorders and food protein-induced enterocolitis. Symptom improvement was established using a previously published questionnaire that ranked gastrointestinal symptoms according to a Likert scale (Appendix 1). This questionnaire was initially completed in clinic at the start of the elimination diet (baseline) and then sent by post at 4 and 8 weeks during their elimination diet and completed via phone interview (17). Data on the assessment of symptom improvement has been published in further detail by Lozinsky et al (18). Once symptom improvement was seen on the elimination diet, parents were sent the Pediatric Quality of Life Inventory (PedsQL^{TM}) proxy questionnaire and the Family Impact Module (FIM) of the PedsQL^{TM} (19) by post. A research appointment was scheduled for researchers to answer any questions about the questionnaire content. Subsequent home food introductions have occurred in all children but this work is yet to be published. Children with non-allergic co-morbidities and those who did not have any symptom improvement during the elimination diet period were excluded.

Materials

The PedsQL™ has been validated for parental proxy use in children above 2 years of age (17). It is scored out of 100 and a higher score represents a better QoL. The Family Impact Module (FIM) PedsQL™ Questionnaire (19) assesses the impact on the HRQoL of the family as a whole (see Appendix 2 for full details of the scales used).

Comparison Groups

Our data was compared to three published control groups who had also used the Parental Proxy PedsQL™ tool to assess HRQoL. The first comparison was made with our cohort to published norm data for this scale (20). The other two groups were children with FAP (mean age = 11.2 years) (15) and those with IgE-mediated peanut allergy (mean age of children = 9.8 years; fathers mean age = 45.33, SD=4.42; mothers mean age = 42.59, SD=4.46) (16). FAP was chosen as it is a gastrointestinal disorder which can present with similar symptoms to GIFA (i.e. abdominal pain) and both can take time to diagnose which is likely to have a significant impact on HRQoL. The IgE group was selected because of the similarities to GIFA, such as food avoidance, difficulties experienced in social situations involving food and anxiety around food exclusions, in spite of the more acute onset of peanut allergy. Comparisons with this group were conducted with non-IgE children aged 5-12 years only in order to ensure age groups of the two cohorts were comparable.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22 (Armonk, NY). Data was checked for skew and kurtosis and was within acceptable levels for normal distribution. One sample t-tests were run to look at differences between PedsQL™ scores for the GIFA group and norm

data. Between-subject t-tests were used to compare PedsQL scores between children with GIFA and the cohorts of children with IgE-mediated food allergy and FAP. The study had 94% power to detect medium effect sizes for one sample t-tests, 50% power for comparisons with the IgE-mediated group and 75% for comparisons with the FAP group. Pearson's correlations were conducted to measure the relationship between Parent Proxy PedsQL™ scores and FIM PedsQL™ scores. A multiple linear regression model was run to assess the relationship between PedsQL™ scores for parents of children with GIFA (outcome variable) and variables that were significantly associated with this measure. All tests were two-sided and significance level was set to 0.05.

Results

A total of 66 children aged 2 to 16 years of age were identified with GIFA, of which 52 parents consented to participate and completed the PedsQL™ proxy questionnaire and the FIM. The questionnaires were mainly completed by mothers (n=43, 82.7%), 3 (5.8%) by fathers and 6 (11.5%) did not specify which parent completed the questionnaire. Demographic data and GIFA characteristics of the children are described in Appendix 3. Over 50% of the patients had up to three foods eliminated and the most common combination of foods eliminated were cow's milk, egg, soya and wheat (26.9%) or cow's milk and soya (26.9%). Of the cohort, 61.5% had at least one comorbidity, with nasal congestion (67.3%) being the most prevalent.

Comparisons between GIFA group PedsQL scores, FIM scores and norm data for the PedsQL

The mean total parental proxy PedsQL™ score for the GIFA cohort was 75.43 (SD=13.82) with the lowest mean score seen in the domain of emotional functioning (mean=67.72, SD=19.58) (Table 1). In comparison to norm data for the PedsQL™, the GIFA cohort had significantly worse physical (t(25)=-

2.36, p=.03), emotional (t(25)=-2.62, p=.02), psychosocial (t(25)=-2.20, p=.04) and total quality of life (t(25)=-2.12, p=.04) (Table 1). Poorer parent rated HRQoL for the child was significantly related to poorer family related QoL (r=0.58, p<0.001).

Comparisons between GIFA, IgE and FAP cohorts

Overall HRQoL and social functioning QoL were significantly better in the GIFA cohort compared to the FAP cohort; however, the GIFA cohort had significantly worse HRQoL scores for emotional functioning (Table 2). In comparison to the IgE cohort, there were no significant differences in overall HRQoL but the GIFA group had significantly poorer QoL for physical functioning (Table 3).

Relationships between GIFA characteristics and quality of life

Univariate analysis showed that the parental proxy total PedsQL^{TM} scores for children with GIFA were significantly related to the number of foods excluded (r=-.38, p=0.006) and scores for gastrointestinal symptoms (r=-.32, p=0.021), abdominal pain (r=-.28, p=0.043), back arching (r=-.40, p=0.003) and flatus (r=-.28, p=0.047) after commencement of the elimination diet. Children with nasal congestion had significantly poorer total QoL (n=35, mean=72.84, SD=14.96) compared to children with no nasal congestion (n=17, mean=80.75, SD=9.40), (t(46.47) =2.32, p=0.025).

When examining relationships between GIFA characteristics and subscales of the PedsQL there were significant correlations between the number of foods excluded and social (r=-.39, p=.005), nursery related (n=16, r=-.74, p=.001) and psychosocial (r=-.33, p=.018) QoL. Severity scores for gastrointestinal

symptoms after commencement of the elimination diet was significantly related to physical (r=-.44, p=.001) and psychosocial (r=-.28, p=.046) QoL. Children with nasal congestion had significantly poorer psychosocial QoL (n=35, mean=72.07, SD=15.30) compared to children without (n=17, mean=80.75, SD=10.55), (t(43.85)=2.41, p=.020). Nursery related QoL was also negatively correlated with the child's age (n=16, r=-.60, p=.013).

Multiple linear regression analysis was conducted with variables that were significantly associated with QoL. The model was significant (F(6,45)=3.37, p=0.008) and explained 31% of the variance (R^2=.31; Adj R^2=.22) in total PedsQL™ HRQoL scores. Factors that had a significant negative impact on the PedsQL™ total scores were the number of foods excluded and nasal congestion (Table 4).

Discussion

This study set out to understand the impact of GIFA on the HRQoL of children as reported by the parents. When compared to the norm data, our cohort had significantly worse total HRQoL scores especially in the physical, emotional and psychosocial functioning domains.

When the GIFA children were compared to the IgE-mediated cohort, there were no significant differences in overall HRQoL; however, our cohort had poorer physical QoL. This may be due to the gastrointestinal symptoms that accompany GIFA including extra-manifestations such as pain, hypermobility and fatigue (21), which can significantly impair QoL that are not common in nut allergies. In our univariate analysis, persistent flatus following an elimination diet was significantly related to quality of life in our cohort, although this association disappeared in the regression analysis possibly due

to this variable being unable to explain any more variance in QoL over and above that of the number of foods and nasal congestion. Lozinsky *et al* (18) found that 26% of participants had flatus as a symptom on dietary elimination. It therefore seems a persistent symptom that could affect quality of life through discomfort, pain and poor sleep (18). There is paucity of data on the impact of flatus on HRQoL in GIFA although in our experience parents reported night waking was common with painful passage of flatus. In an adult study where 71% had flatulence, the presence of gastrointestinal symptoms was reported to have a negative impact on HRQoL (22). In a study by Abaci et al., mothers of infants with infantile colic defined as unexplained, inconsolable crying often accompanied with flushing of the face, drawing-up of the legs and passing of gas, reported poorer HRQoL especially in the domains of physical and social functioning (23). Our results also showed a significant negative impact on physical functioning in association with the severity of gastrointestinal symptoms (i.e. abdominal pain, back arching, flatus) post elimination diet.

Emotional functioning was reported as the domain of HRQoL that parents felt their children with GIFA were most affected by and scores were significantly poorer than norm population data and children with FAP. Although not previously described for GIFA, feelings of anxiety and worry in children with food allergy has been well documented, with several studies on children with IgE-mediated peanut allergy reporting lower emotional health scores compared to children without food allergy (1, 16, 24). Poorer emotional HRQoL may be related to the children with GIFA experiencing emotional distress related to environments involving food or associating symptoms (i.e. abdominal pain, vomiting) with eating specific foods. Delays in diagnosis due to the absence of diagnostic tests for GIFA, which can lead to prolonged symptoms, may also have an impact on the emotional psychological health of children.

Emotional functioning can also be affected by quality of sleep or sleep deprivation (25). Previous studies with children affected by other atopic conditions (e.g. asthma, eczema) have shown that there is an increase in nocturnal awakening and disturbed sleep (26, 27). Poor sleep has been reported in approximately one third of patients with GIFA (21), which can impact their emotional health. Over half of our cohort had nasal congestion, which can be a manifestation of allergic rhinitis (28). This comorbidity may have an effect on sleep which could explain the lower scores we found in these children; however, this link requires further research.

Eliminating multiple foods was found to have a negative correlation with HRQoL in our cohort, which has also been reported in children with IgE-mediated food allergy (2). It has been shown that anxiety increases in children if food elimination includes two or more foods (29) and this could have contributed to the poorer emotional HRQoL seen in our cohort.

We found that poorer HRQoL in the child was related to a bigger impact on the whole family. This is a similar finding to that of Greenhawt *et al* (3030) where the HRQoL of carers of children with Food Protein-induced Enterocolitis Syndrome (FPIES), a type of GIFA, was compared to carers of children with IgE-mediated food allergies. Although they used a different questionnaire (Food Allergy Quality of Life – Parental Burden (FAQL-PB) Index), they found that carers of children with FPIES reported significantly worse QoL compared to those of children with IgE-mediated food allergy but also that the FAQL-PB scores correlated strongly with PedsQL-FIM scores.

Limitations

This study had several limitations. Firstly, GIFA was diagnosed following symptom improvement after an elimination diet but was not confirmed with a follow up re-introduction challenge. Therefore, it is not a challenge-proven diagnosis. Secondly, the parent proxy PedsQL^{TM} is designed to be used in children at least 2 years old. In our cohort, there were a number of children who were less than 2 years old and as there was no tool available to assess their quality of life they were excluded. There was also no prospective control group available for us to compare our data to. Although the PedsQL^{TM} is designed to be used for all types of diseases, it has not been specifically validated for parent proxy use for children with GIFA. GIFA can often start in infancy; thus developing a tool that allows for more specific GIFA disease-specific questions is important, but validating it for use by parents for younger children, unable to complete questionnaires themselves, is also necessary.

Another limitation is that we used two historical comparison groups in our study where the children had different diseases and were recruited and interviewed by researchers differently. Although we tried to find cohorts that had some effects of quality of life that would be similar to children with GIFA, all chronic diseases have unique clinical features that can directly impact HRQoL and trying to make comparisons between diseases that are potentially different, can be challenging. We also had very few fathers take part in our study and future work should consider encouraging more fathers to give their views about the impact on quality of life.

Due to the small sample sizes our study was underpowered to detect small effects and there may be more differences between these groups than we have been able to find. In contrast to this, there is also the risk that we have made a Type I error and reported false positive differences due to the number of tests we ran. As this is the first study to report on the impact of GIFA on QoL in comparison to other

similar chronic conditions, we felt it important to report all differences found so that future research can build upon these findings in robust and properly powered studies.

Conclusions:

This study has found that parent reported HRQoL of their children with GIFA was worse compared to a normal population. However, when compared to children with IgE-mediated allergy or FAP, only the domains of physical and emotional functioning, respectively, were significantly worse. The number of foods excluded, severity of gastrointestinal symptom scores and the presence of nasal congestion had a significant negative impact on total HRQoL score. Proxy parental HRQoL scores are useful; however, the development of a questionnaire that allows for specific assessment of children with GIFA of all ages is needed to better understand the impact of this disease on children's lives.

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Table 1: Proxy PedsQL^{TM} scores of children with GIFA in different domains and norm data

	Non-IgE cohort			Norm data
	N	Mean	SD	Mean
Nursery functioning (2-4 years)	16	72.40	19.65	N/A
School functioning (≥5 years)	33	73.18	18.06	78.19
Emotional functioning	51	67.72	19.58	81.04*
Physical functioning	51	77.56	16.12	84.37*
Social functioning	52	83.85	15.07	86.82
Psychosocial functioning	52	74.94	14.43	82.11*
Total Score	52	75.43	13.82	82.79*

*$p<0.05$

Table 2: Comparison of quality of life between the GIFA cohort and the FAP cohort

	Non-IgE-mediated cohort			Functional Abdominal Pain Cohort			Mean difference	p-value
	N	Mean	SD	N	Mean	SD		
School (≥5 y)	33	73.18	18.06	65	72.2	15.80	-1.0	0.78
Emotional	51	67.72	19.58	65	75.20	18.10	7.5	**0.04**
Physical	51	77.56	16.12	65	76.94	11.80	-0.7	0.80
Social	52	83.85	15.07	65	67.10	12.30	-16.8	**<0.001**
Psychosocial	52	74.94	14.43	65	§	§	§	§
Total average	52	75.43	13.82	65	70.10	7.90	-5.3	**0.01**

§ - Assessment not performed in FAP by Youseef *et al*. (17)

Table 3: Comparison of quality of life between the GIFA cohort aged 5-12 years and the IgE cohort

	Non-IgE-mediated cohort			IgE-mediated cohort			Mean difference	p-value
	N	Mean	SD	n	Mean	SD		
Physical	26	77.37	15.08	44	89.92	11.41	12.55	**<0.001**
Emotional	26	70.96	19.65	44	70.45	19.37	-.51	.92
Social	27	82.96	15.83	44	81.93	15.67	-1.03	.79
School (≥5 y)	27	72.78	18.83	44	77.50	19.30	4.72	.32
Psychosocial	27	75.49	15.65	44	76.93	16.20	1.44	.72
Total average	27	76.01	14.40	44	81.27	13.58	5.26	.13

Table 4. Regression analysis to examine associations between non-IgE characteristics and total PedsQL scores.

Predictors	Unstandardised Coefficients		Standardised Coefficients	95% Confidence intervals	
	B	Standard Error	Beta	Lower	Upper
Number of foods excluded	-2.34	.90	**-.33****	-4.15	-.52
Gastrointestinal symptom	.21	.55	.09	-.89	1.32
Abdominal pain	-3.42	4.41	-.12	-12.31	5.47
Back arch	-6.78	5.82	-.18	-18.50	4.93
Flatus	-6.00	5.12	-.22	-16.30	4.32
Nasal congestion	-8.03	3.70	**-.28***	-15.49	-.57

*p<.05, **p<.01