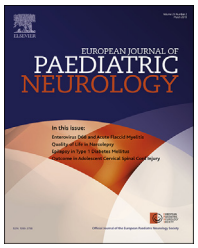
Official Journal of the European Paediatric Neurology Society



Original article

A population-based and case-controlled study of children and adolescents with narcolepsy: Health-related quality of life, adaptive behavior and parental stress

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ARTICLE INFO

Article history:
Received 24 July 2018
Received in revised form
17 December 2018
Accepted 10 January 2019

Keywords:
Child
Adolescent
Health-related quality of life
Adaptive behavior
Parenting stress
Narcolepsy

ABSTRACT

Objective: To investigate health-related quality of life (HrQoL) and adaptive behavior in young people with narcolepsy and stress among their parents.
Methods: In a cross-sectional exploratory quantitative study design, 37 young people with narcolepsy (8–20 years of age) and their parents were recruited. Thirty-one had post-H1N1 vaccination-related narcolepsy (PHV) and six had narcolepsy not related to PHV (nPHV). In addition, 40 age- and gender-matched controls (aged 5–20 years) were recruited.
Results: Thirty-one patients completed the generic HrQoL questionnaire KIDSCREEN and the disease-specific NARQoL-21. HrQoL was found to be significantly diminished in all domains in the PHV group ($p = 0.001$) and in the School/Concentration domain ($p = 0.004$) in the nPHV group compared to age- and gender-matched controls. The Adaptive Behavior Assessment System was completed by parents of 32 patients. They rated their children significantly lower in the General adaptive composite ($p = 0.026$) and the Conceptual ($p = 0.050$) and Social composite scores ($p = 0.001$) compared with reference data on healthy Swedish children's and young people's adaptive behavior. Parents of 36 patients filled in the 36-item short form of the Parenting Stress Index questionnaire. They rated significantly higher Total stress, Parent-child dysfunctional interaction, and Difficult child scores compared with parents of controls ($p = 0.001$, $p = 0.005$, $p < 0.001$).
Conclusions: Children with narcolepsy have diminished HrQoL compared with controls. Parents of children with narcolepsy experience impaired adaptive behavior in their

Abbreviations: ABAS-II, Adaptive Behavior Assessment System, Second Edition; CHQ, Child Health Questionnaire; HrQoL, Health-related quality of life; NARQoL-21, Narcolepsy Quality of Life 21-item questionnaire; nPHV, non-post-H1N1 influenza vaccination narcolepsy; NS, non-significant; PHV, post-H1N1 influenza vaccination narcolepsy; PSI/SF, Short form of Parenting Stress Index; VSP-A, Vécu et Santé Perçue de l'Adolescent; VSP-E/P, Vécu et Santé Perçue de l'Adolescent - child/parent version.

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https://doi.org/10.1016/j.ejpn.2019.01.004

children and high levels of parenting stress. Identifying the contributory factors is necessary, and early intervention is crucial in order to improve the HrQoL of these children and their families.

1. Introduction

Narcolepsy is a lifelong, disabling sleep disorder with typical onset of symptoms in the second decade of life.[1] It is characterized by excessive daytime sleepiness, sleep attacks, cataplexy, hypnagogic and hypnopompic hallucinations, sleep paralysis, and disturbed nighttime sleep. The prevalence of narcolepsy in childhood has been estimated to be 0.06% and the incidence 0.96–2.35/100,000.[2,3] In a population-based study of children and adolescents in western Sweden, we found a 25-fold increase in the childhood incidence of narcolepsy in relation to the H1N1 influenza vaccination with Pandemrix during 2009–2010.[2,4] In a follow-up study of these patients, we also found an increased psychiatric comorbidity compared to the general healthy child population.[5]

Several studies have addressed HrQoL in adults with narcolepsy. Three of these studies included 502 adult patients and reported decreased HrQoL in all domains[6–8] and one of which suggested difficulties with school achievement in childhood in 55% of the patients.[6] Only two studies have been performed in children and adolescents with narcolepsy.[8,9] Neither of these studies have used disease-specific HrQoL instruments. In the first study, the Child Health Questionnaire (CHQ) was used on 42 children (4–18 years) and a significant difference was found in the mental health subscale but not in physical health or global health subscales compared with controls.[9] In the second study, HrQoL was assessed in 117 children (5–17.5 years) using a questionnaire adapted for adolescents, the Vécu et Santé Perçue de l'Adolescent (VSP-A) and a version for parent report in the younger children, the VSP-E/P.[10] It was found that, in general, the enrolled patients had significantly lower general well-being, social skills, and school performance.[10] Moreover, children with narcolepsy had significantly lower vitality, lower general well-being, and poorer self/body image, while adolescents with narcolepsy had significantly lower physical well-being compared to age-matched controls, although psychological well-being was not significantly affected. Depressive symptoms, measured with the Children's Depression Inventory, were also assessed in this study and were shown to be highly correlated with lower HrQoL.[10] A retrospective hospital-based study including 42 children (4–18 years) and a cross-sectional study including 51 children (10–17 years) have also described social difficulties and poor school performance in a large proportion of children with narcolepsy.[9,11] These impairments could affect adaptive functioning, which is defined as the cognitive, social, and practical skills an individual uses to adapt to the demands of the environment, such as communication and learning.[12,13] Adaptive behavior, measured by the Child Behavior Checklist (CBCL) parent report form, has been investigated in a group of 12 children (7–16 years) with narcolepsy.[14] These children had lower competence than the general population on the Total Score Index and on the subscales of school, activity, and social competence.

Decreased HrQoL and poor adaptive functioning are likely to have an effect on the child–parent relationship. Increased parenting stress has been reported in relation to children with chronic diseases such as epilepsy (65 children; 9–12 years), attention deficit hyperactivity disorder (ADHD) (43 children; 7–12 years), and obstructive sleep apnea (115 children; 3–5 years) but has not been studied in children with narcolepsy.[15–17]

Given the impairments indicated by these studies we set out to analyze the level of disease-specific HrQoL and adaptive functioning in a well-defined cohort of patients with narcolepsy compared with age- and gender-matched controls. Our hypotheses were that children with narcolepsy would exhibit lower HrQoL, be impaired in adaptive functioning and that parents of children with narcolepsy would experience greater parenting stress. An additional hypothesis was that patients with post-H1N1 influenza vaccination narcolepsy (PHV) would have lower HrQoL, adaptive functioning and their parents greater parenting stress than patients with narcolepsy who had not received the H1N1 influenza vaccination (nPHV).

2. Materials and methods

2.1. *Subjects*

The study group consisted of 34 children and three young people with a mean age of 13.9 years (SD 4.1; range 8–20) (Table 1). All the patients were recruited from western Sweden and had onset of narcolepsy between January 1, 2000 and December 31, 2010. The population based study design was possible since all patients in the two included counties was identified and included in the study.

Patient selection was based on the diagnostic criteria for narcolepsy according to the International Classification of Sleep Disorders – Second Edition (ICSD-2, 2005) and Third Edition (ICSD-3, 2014).[18,19] The study group included 31 patients with post-H1N1 influenza vaccination narcolepsy (PHV) and six patients with narcolepsy who had not received the H1N1 influenza vaccination (nPHV). All but one patient fulfilled the diagnostic criteria for Narcolepsy type 1. The patient with Narcolepsy type 2 had no cataplexy and had a CSF Hypocretin-1 level at 121 pg/ml. All but one patient have been investigated with MSLT (Table 1). The patient which has not been investigated with MSLT fulfilled the diagnostic criteria

Table 1 – Demographics, clinical and laboratory characteristics in children and adolescents with narcolepsy.

Characteristics		nPHV group (N = 6)	PHV group (N = 31)	Total number of patients
Gender	Female	5/6	15/31	20/37
	Male	1/6	16/31	17/37
Symptoms	Cataplexy	6/6	26/31	32/37
	Hallucinations	5/6	14/31	19/37
	Sleep paralysis	3/6	10/31	13/37
	Disturbed sleep	6/6	23/31	29/37
Psychiatric comorbidity	Major depression[a]	0/6	6/30	6/36[b]
	ADHD, predominantly inattentive type[c]	1/4	8/28	9/32[b]
	General anxiety disorder	0/6	3/30	3/36[b]
	Oppositional defiant disorder	1/6	2/30	3/36[b]
	Pervasive developmental disorder - not otherwise specified	0/6	1/30	1/36[b]
	Eating disorder - not otherwise specified (anorectic type)	0/6	1/30	1/36[b]
Actigraphy/MSLT	Positive	6/6	26/30	32/36[b]
HLA-DQB1*0602	Negative	1/4	0/22	1/26[b]
	Positive	3/4	22/22	25/26[b]
CSF Hypocretin-1	>110 pg/ml	0/4	1/28	1/32[b]
	<110 pg/ml	4/4	27/28	31/32[b]
Treatment	Methylphenidate	4/6	28/31	32/37
	Atomoxetine	1/6	0/31	1/37
	Modafinil	1/6	1/31	2/37
	Antidepressants	3/6	7/31	11/37
	Sodium oxybate	0/6	1/31	1/37
	No treatment	1/6	1/31	2/37

Abbreviations: PHV, post-H1N1 influenza vaccination narcolepsy; nPHV, non-post-H1N1 influenza vaccination narcolepsy; ADHD, attention deficit hyperactivity disorder; CSF, cerebrospinal fluid; MSLT, multiple sleep latency test. Actigraphy was always performed before MSLT.

[a] Of six patients with major depression, one fulfilled DSM-IV criteria for major depression including functional decline, but some of the criteria overlapped with symptoms of narcolepsy.

[b] The number of patients was less than 37 because not all patients needed all investigations to fulfill the criteria for narcolepsy according to ICSD 2005 and ICSD 2014.

[c] With inception after onset of narcolepsy and above 7 years of age, all patients had inattentive type ADHD. Overlapping of psychiatric diagnoses occurred in seven patients.

for Narcolepsy type 1 owing to present of excessive daytime sleepiness, cataplexy and hypocretin level below 110 pg/ml. The mean disease duration was 2.6 years (SD 0.5, range 1.9–3.8) in the PHV group and 6.5 years (SD 2.4, range 3.4–9.7) in the nPHV group. PHV narcolepsy was defined as clinical onset within 10 months of vaccination. For the evaluation of HrQoL, we used age- and gender-matched controls who were healthy friends and school companions recruited from the same counties, and parenting stress was measured in the parents of both patients and controls. Not all the patients completed all sections of each questionnaire; the number of completed questionnaires is indicated in Tables 2–4.

Psychiatric comorbidity was diagnosed in thirteen patients who have participated in a previously study using a test battery of semi-structured interviews generating DSM-IV diagnoses, including the development and well-being assessment (DAWBA) and the attention deficit/hyperactive disorder-rating scale (ADHDRS). The autism spectrum screening questionnaire (ASSQ) and the positive and negative syndrome scale (PANSS) were used to screen for autistic traits and psychotic symptoms respectively.[5]

2.2. Instruments

2.2.1. Health-related quality of life

For the measurement of HrQoL, the KIDSCREEN-10 and NARQoL-21 questionnaires were used.[20–22] The KIDSCREEN-10 self-report questionnaire is a standardized instrument for screening, monitoring, and evaluation of HrQoL with regard to physical, mental, and social well-being. It is validated for children and adolescents aged 8–18 years. The mean index score across Europe is 47.45 (SD = 9.73) on a 0–100 scale in a healthy school-age population.[23] NARQoL-21 is a self-reported narcolepsy-specific HrQoL questionnaire for children and adolescents.[22] The item list was developed from the expressed views of children and adolescents with narcolepsy, aged 8–18 years. NARQoL-21 includes two factors, five domains, and 21 items.[22] The first factor is *Psychosocial* with 15 items assigned to three domains: *Emotional reaction*, *Social confidence*, and *School/Concentration*. The second factor is *Future outlook* with 6 items assign to two domains: *Expectations* and *Limitations*. Each of the items is answered by the patient on a five-point Likert scale from completely untrue to completely true. The summated rating method is used for each domain and, for ease of interpretation, the raw scores are transformed to a 0–100 scale in which higher scores indicate better narcolepsy-specific HrQoL. A score below 42 indicates a suboptimal HrQoL, with a sensitivity of 84% and a specificity of 92%.

2.2.2. Adaptive behavior

To assess the adaptive function skills, the Swedish version of the Adaptive Behavior Assessment System version 2 (ABAS-II) was used.[13] The ABAS-II provides a comprehensive assessment of the adaptive behavior of individuals aged 5–21 years.

Table 2 – Health-related quality of life in children and adolescents with narcolepsy.

Investigated health areas			PHV group				nPHV group			
			Narcolepsy patients	Control group			Narcolepsy patients	Control group		
			N	Median (Q1–Q3)	N	Median (Q1–Q3)	p-value	N	Median (Q1–Q3)	N	Median (Q1–Q3)	p-value
Health-related quality of life	KIDSCREEN NARQoL-21		27	65 (56–78)	29	83 (75–92)	<0.001	4	60 (60–60)	11	85 (75–91)	0.081
		Emotional reaction	27	75 (50–88)	29	94 (81–100)	<0.001	4	75 (23–93)	11	90 (74–93)	NS
		Social confidence	27	75 (56–81)	29	88 (81–98)	0.001	4	81 (75–97)	11	88 (75–100)	NS
		School/Concentration	27	69 (44–94)	29	94 (88–100)	<0.001	4	66 (39–78)	11	63 (56–69)	0.004
		Expectations	27	63 (42–75)	29	92 (75–100)	<0.001	4	75 (29–88)	11	83 (83–100)	NS
		Limitations	27	67 (42–83)	29	88 (75–92)	<0.001	4	92 (63–100)	11	100 (100–100)	NS

KIDSCREEN and NARQoL-21 questionnaires were completed by patients with narcolepsy. The different main domains and subdomains are reported with median values. Statistical comparisons were performed with the mean scale score for the age- and gender-matched control groups. The accepted level of statistical significance was $p < 0.05$.
Abbreviations: PHV, post-H1N1 influenza vaccination narcolepsy; nPHV, non-post-H1N1 influenza vaccination narcolepsy; NARQoL-21, Narcolepsy Quality of Life 21-item questionnaire; NS, non-significant; Q, quartiles.

Table 3 – Parent-reported adaptive behavior in children and adolescents with narcolepsy.

Investigated health areas			PHV group				nPHV group			
			Narcolepsy patients	Control group			Narcolepsy patients	Control group		
			N	Median (Q1–Q3)	N	Median	p-value	N	Median (Q1–Q3)	N	Median	p-value
Adaptive behavior (ABAS-II)	General adaptive composite		28	94 (77–108)	–	100	0.026	4	106 (94–120)	–	100	NS
	Conceptual	Total conceptual score	28	95 (75–105)	–	100	0.05	4	104 (85–117)	–	100	NS
		Communication	28	9 (8–11)	–	10	NS	4	11 (8–12)	–	10	NS
		Functional Academics	28	11 (6–12)	–	10	NS	4	12 (10–12)	–	10	NS
		Self-direction	28	8 (4–10)	–	10	0.001	4	10 (6–13)	–	10	NS
	Social	Total social score	28	89 (75–99)	–	100	0.001	4	102 (86–114)	–	100	NS
		Social	28	9 (6–11)	–	10	0.015	4	11 (8–12)	–	10	NS
		Leisure	28	7 (3–10)	–	10	0.001	4	11 (7–13)	–	10	NS
	Practical	Total practical score	28	93 (83–114)	–	100	NS	4	116 (95–120)	–	100	NS
		Community use	28	9 (7–12)	–	10	NS	4	12 (11–13)	–	10	NS
		Home living	28	7 (3–11)	–	10	0.004	4	13 (10–15)	–	10	NS
		Self-care	28	10 (5–12)	–	10	NS	4	11 (7–12)	–	10	NS
		Health and safety	28	12 (9–13)	–	10	0.074	4	14 (10–17)	–	10	NS

Adaptive behavior was rated by parents using the second version of the Swedish Adaptive Behavioral Assessment Scale (ABAS-II). The different adaptive behavior composites and skill areas are reported with median values. Comparisons were performed with the mean scale score for a Swedish healthy pediatric reference population, with a mean of 100 for the adaptive behavior composites and 10 for the skill areas. The accepted level of statistical significance was $p < 0.05$.
Abbreviations: PHV, post-H1N1 influenza vaccination narcolepsy; nPHV, non-post-H1N1 influenza vaccination narcolepsy; ABAS-II, Adaptive Behavior Assessment System, Second Edition; NS, non-significant; Q, quartiles.

The children's abilities are rated by their parents in nine different skill areas reflecting different aspects of adaptive behavior, namely *Communication*, *Community use*, *Functional academics*, *Home living*, *Health and safety*, *Leisure*, *Self-care*, *Self-direction*, and *Social skills*. Each skill area has a scaled score mean of 10, with a standard deviation of 3. The skill areas are grouped into three adaptive composites, *Conceptual* (Communication, Functional academics, Self-direction), *Social* (Leisure, Social), and *Practical* (Community use, Home living, Health and safety, Self-care), with a standard score mean of 100 and a standard deviation of 15. All nine skill areas are also combined into a General adaptive composite (GAC), with a standard score mean of 100 and a standard deviation of 15, which reflects the individual's overall adaptive functioning. Reference data on the adaptive behavior of healthy Swedish children and young people was used for comparison with the adaptive behavior of children and young people with narcolepsy.

2.2.3. *Parenting stress*

Parenting stress was evaluated with the short form of Parenting Stress Index (PSI/SF) consisting of 36 questions screening for stress in the parent–child relationship.[24] The PSI/SF yields a Total stress score from three scales: *Parental distress* (self-esteem in parents), focusing on the parental distress and anguish that the father and/or mother experience in their roles as parents, *Parent–child dysfunctional interaction* (parent–child interaction), focusing on the parents' perception of their child and the extent to which the child meets the

Table 4 – Parenting stress in the parents of children and adolescents with narcolepsy.

Investigated health areas		PHV group					nPHV group				
		Narcolepsy patients		Control group			Narcolepsy patients		Control group		
		N	Median (Q1–Q3)	N	Median (Q1–Q3)	p-value	N	Median (Q1–Q3)	N	Median (Q1–Q3)	p-value
Parenting stress (PSI/SF)	Total stress score	30	87 (65–104)	25	63 (50–69)	0.001	5	74 (48–83)	12	55 (48–70)	NS
	Parental distress	31	24 (17–29)	26	21 (17–25)	NS	5	17 (16–22)	12	21 (15–25)	NS
	Parent–child dysfunctional interaction	30	25 (19–37)	26	17 (14–24)	0.005	5	21 (15–29)	12	17 (13–21)	NS
	Difficult child	30	35 (29–43)	25	21 (16–28)	<0.001	5	31 (18–36)	12	20 (14–27)	NS

The short form of the Parenting Stress Inventory (PSI/SF) was completed by the parents. Median values were compared with the mean score of the age- and gender-matched control groups. The accepted level of statistical significance was $p < 0.05$.
Abbreviations: PHV, post-H1N1 influenza vaccination narcolepsy; nPHV, non-post-H1N1 influenza vaccination narcolepsy; PSI/SF, Parenting Stress Inventory; NS, not significant; Q, quartiles.

parents' expectations, and *Difficult child* (child self-regulation), focusing on the parents' perception of behavioral characteristics of children that make their child either easy or difficult to manage. Higher scores indicate higher levels of stress.

2.3. Ethics

This study was approved by the Regional Board of Medical Ethics at the University of Gothenburg and written informed consent was obtained from all parents, patients and controls participating in the study.

2.4. Statistical analysis

Data processing was performed with IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp.). A significance level of $p < 0.05$ was used for all analyses. The statistical calculations of the adaptive skills were performed with the non-parametric one-sample Wilcoxon test. The comparison of the different variables within KIDSCREEN-10, NARQoL-21, ABAS and PSI between patients in PHV and nPHV groups, males and females and patients with and without psychiatric comorbidity was performed using the non-parametric Mann–Whitney U test. The Pearson correlation coefficient was used to measure the correlation between age and the different variables within KIDSCREEN-10, NARQoL-21, ABAS and PSI.

3. Results

3.1. Health-related quality of life

The self-report questionnaires were completed by 27 of 31 patients in the PHV group (14 girls, mean age 15.1 years, SD 3.9, range 8–20), four of six patients in the nPHV group (three girls, mean age 15.5 years, SD 1.9, range 13–17), and nine of 13 patients with psychiatric comorbidity. There were 29 age- and gender-matched controls for the PHV group (15 girls, mean age 13.0 years, SD 3.3, range 8–19) and 11 controls (six girls, mean age 16.0 years, SD 2.3, range 11–20) for the nPHV group.

Generic HrQoL measured with KIDSCREEN was significantly decreased in the PHV group ($p < 0.001$) compared to the control group. The disease-specific NARQoL-21 scores were significantly lower in all five domains in the PHV group ($p = 0.001$), whereas only the School/Concentration domain was significantly lower ($p = 0.004$) in the nPHV group compared with controls (Table 2). No gender differences were found in either of the PHV or nPHV groups. Patients with psychiatric comorbidity in the PHV and nPHV groups had significantly decreased disease-specific HrQoL compared to patients without psychiatric comorbidity in the same groups (NARQoL Emotional reaction: $p = 0.039$; NARQoL Social confidence: $p = 0.042$). There was no difference in the KIDSCREEN index between patients with or without psychiatric comorbidity ($p = 0.058$).

3.2. Adaptive behavior

The ABAS-II questionnaire was completed by the parents of 28 of 31 patients in the PHV group (13 girls, mean age 13.9 years, SD 4, range 6–19) and four of six patients in the nPHV group (three girls, mean age 15.5 years, SD 1.9, range 13–17).

In the PHV group, the General adaptive composite score was significantly lower ($p = 0.026$) compared with the control group. This finding was repeated in the total Conceptual ($p = 0.05$) and Social ($p = 0.001$) composite scores (Table 3) and also at the level of skill areas: Self-direction skills ($p = 0.001$), Leisure skills ($p = 0.001$), Social skills ($p = 0.015$) and Home living ($p = 0.004$). No significant differences were found between the adaptive behavior skills of the patients in the nPHV group and the control group. When we looked at gender differences, there were no differences in the General adaptive composite or in the Practical composite scores. In the PHV group, the Social adaptive composite score was lower in boys than girls ($p = 0.017$). No age-related differences were seen. The parents of nine (four girls) of 13 patients with psychiatric comorbidity in the PHV and nPHV groups completed the ABAS-II questionnaire. They had lower Conceptual composite scores ($p = 0.036$) compared to patients without psychiatric comorbidity in the same groups.

3.3. Parenting stress

Completed questionnaires were returned from the parents of all 31 patients in the PHV group (14 girls, mean age 13.4 years,

SD 3.9, range 5–19) and the parents of five of six patients in the nPHV group (three girls, mean age 16.3 years, SD 3.4, range 11–20). There were 26 age- and gender-matched controls (11 girls, mean age 13.0 years, SD 4.3, range 5–20) for the PHV group and 12 controls (seven girls, mean age 15.0 years, SD 3.4, range 11–20) for the nPHV group.

Parents of children in the PHV group had higher stress scores in all domains except Parental distress compared to controls. All stress scores except Parental distress were also found to be higher in the nPHV group compared with controls but without reaching statistical significance (Table 4). There was no significant difference in terms of parenting stress experienced by the parents of children with a psychiatric comorbidity than those parents of children with narcolepsy without a psychiatric comorbidity. Neither gender nor age of the children had an effect on parenting stress ratings.

4. Discussion

4.1. *Health-related quality of life in narcolepsy*

To our knowledge, this is the first study to address HrQoL in narcolepsy with a disease-specific validated questionnaire. A well-known advantage of a disease-specific measure is a higher sensitivity for detection and quantification of specific symptoms such as staying awake in school or on public transport. Symptoms that are important to patients with narcolepsy and their clinicians but less frequent in other conditions.[25] Hence disease specific instruments are frequently found to be more clinically responsive to change than generic QOL measures which do not focus on the patients experience of a specific condition.[26]

The NARQoL-21 disease-specific measure can identify outcomes from the perspective of the children themselves and also be more easily translated into clinical practice as compared with information derived from generic questionnaires.[27] The previous retrospective and cross-sectional multicenter studies in children with narcolepsy used generic questionnaires, namely the 50-item CHQ and the VSP-A and VSP-E/P).[9,10] We identified significantly diminished HrQoL in all children with narcolepsy in the PHV group measured with both the generic KIDSCREEN and the disease-specific NARQoL-21. Only the School/Concentration domain was significantly lower in the nPHV group compared with controls (Table 2). Comparison between these groups is difficult due to the small number of patients, especially in the nPHV group (Table 2). The fact that the previous two studies in children and adolescents with narcolepsy used different questionnaires than those in our study limits our ability to make direct comparisons. Our findings of diminished HrQoL in the Emotional reaction domain is similar to the study using the CHQ,[9] and the decreased HrQoL in Social confidence and School/Concentration domains is similar to the study using the VSP-A and VSP-E/P.[10] We identified lower scores in all domains, giving the impression of a more global impact on HrQoL. One possible explanation could be that we used a disease-specific questionnaire, which is more sensitive to the effects of narcolepsy on HrQoL. Another explanation could be the high number of patients in our study who had received the H1N1 influenza vaccine (82%); this compares to 32% in the study using the VSP-A and VSP-E/P and none in the study using the CHQ.[9,10] Narcolepsy associated with the H1N1 influenza vaccination is known to have a more sudden onset and a more severe course, which could lead to a greater effect upon HrQoL.[28,29] A more global impact on HrQoL, in both the Emotional reaction and Social confidence domains, has also been reported in several studies in adults with narcolepsy.[6,7] The diminished HrQoL in the School/Concentration domain compared to healthy controls was seen in both our study and the study using the CHQ.[9] Educational problems, problems retaining employment, and lower employment rates have been described in adults with narcolepsy.[8] This is possibly related to lower school performance due to difficulties with attention, working memory, and verbal comprehension, as shown in a previous study of the same cohort of patients.[5] Another possible contributing factor identified in the same study is psychiatric comorbidity. In the same cohort of patients, we previously described that 43% of patients had psychiatric comorbidity, 29% had ADHD of the predominantly inattentive type, 20% had major depression, and 10% had general anxiety disorder.[5] All patients had onset of psychiatric disorder after onset of narcolepsy.[5] In these cases, a negative add on effect of psychiatric comorbidity on the HRQoL could be suspected. Depressive feelings, hyperactivity, anxiety, and conduct problems have been shown to influence HrQoL in both children and adults with narcolepsy.[9,10,30] Impaired neurotransmitter interactions of the hypocretinergic neurons with frontal cortex, amygdala, and serotonergic neurons in the brainstem could explain the associated psychiatric comorbidity and cognitive difficulties.[31–33] We found that in the group with psychiatric comorbidity there was a decrease in the NARQoL domains Emotional reaction, Social confidence, and School/Concentration compared to those with narcolepsy without psychiatric comorbidity, as predicted by previous studies. Adult patients diagnosed with narcolepsy tend to have lower HrQoL compared to patients with other sleep disorders, which might suggest additional mechanisms other than decreased daytime functioning due to disturbed nighttime sleep such as psychiatric comorbidity.[34]

We also investigated the concept of the individuals' future outlook in relation to HrQoL. The two NARQoL-21 domains within this factor, Expectations and Limitations, showed significantly lower scores compared with controls. This is of crucial importance considering that HrQoL is related to the "belonging, being, and becoming" of an individual and that adolescents are particularly vulnerable to health conditions that will impose limitations concerning their plans for the future.[35] Thus, our findings highlight the importance of achieving optimal social and educational support during the childhood of young people with narcolepsy in order to meet appropriate future goals. Their anxiety about the future, illustrated by the lower scores in the two future domains, is confirmed in several studies of adults with narcolepsy, where lower socio-economic standards, lower rate of employment, lower rate of marriage, and more frequent health care service contacts are seen.[8,30]

4.2. *Adaptive behavior*

Standardized assessments of the behavior and adjustment problems experienced by young people with narcolepsy have not been undertaken previously. The General adaptive composite score and the total scores of Conceptual and Social composites, as measured by the ABAS questionnaire, were significantly lower in the PHV group compared with controls. These adjustment problems can be seen in relation to our findings of a decrease in the School/Concentration and Social confidence domains in the disease-specific NARQoL-21 questionnaire, confirming the problems experienced at school by these children. In studies of children with narcolepsy and other sleep disorders, issues related not only to behavior but also to mood, attention, and educational challenges have been found.[9,11,14,36] This is in line with the findings in our study and it highlights the psychological and social problems experienced by young people with narcolepsy.

4.3. *Parenting stress*

The parents of all the children in the PHV group had higher Total stress scores compared to controls. Neither gender nor age of the children had an effect on parenting stress ratings. One previous study has addressed the impact of narcolepsy on the family using the Strengths and Difficulties Questionnaire, which focuses on behavioral problems.[8] The study found a significantly higher impact on the family in both children with narcolepsy and children with excessive daytime sleepiness compared with controls.[9] Increased impact in all domains of the PSI/SF has been reported in children with other sleep disorders, such as obstructive sleep apnea with the strongest impact on the children's behavior.[17] The findings of these previous studies are consistent with our findings of increased parenting stress scores. In our study we found that parenting stress was related to how the parents conceptualized a difficult child and a parent–child dysfunctional interaction.

5. Limitations and strengths

Comparison between groups in this study is difficult due to the small number of individuals, especially in the nPHV group. Because of this, we found it important to obtain different perspectives on the patients' situation. In our assessment of the patients' HrQoL we have relied upon the report of the patients themselves. However, as consistency between parent and patient ratings of HrQoL in children and adolescents with narcolepsy has previously been shown to be good,[9] obtaining parental HrQoL ratings in this study could have yielded useful additional information. A weakness in the methodology is that the PSI/SF questionnaire is validated for children up to 12 years of age and not for adolescents. Despite this, the PSI/SF is the most frequently used questionnaire internationally,[37] and we considered the questions to be relevant even to the families with children older than 12 years. The major strengths of this study are the population-based study design and the use of age- and gender-matched control groups. Another strength in our study is the validated disease-specific NARQoL-21 questionnaire, which has been shown to be more sensitive to identifying issues than the generic KIDSCREEN questionnaire. KIDSCREEN was chosen as a validation instrument due to its psychometric qualities and proven validity in many languages. The short version of provides one measure of quality-of-life which is a multidimensional construct. Behind the construct in Kidscreen are questions drawn from the domains of Physical and Emotional well-being, Family and Social relationships and School which closely maps the NarQoL-21. In general however, the difference between an illness specific and generic questionnaire is in the choice of these dimensions and the questions used to measure them. Illness specific instruments focus on the issues relevant the target population whereas generic instruments may include dimensions of less or no relevance to the target population. In the case of narcolepsy, aspects of QoL related to expectations and limitations of the future are completely missing from most generic QoL instruments. Furthermore, psychiatric comorbidity in the study population was well described in an earlier study, which made it possible to discuss its impact on HrQoL, adaptive behavior, and parenting stress. In this context, our results speak to the superiority of the NarQoL-21 to detect differences in HrQoL between children with and without psychiatric comorbidity.

6. Conclusions

This is the first population-based study to look at HrQoL and adaptive behavior in children and adolescents with narcolepsy and parenting stress among their parents. Our main finding is that there is diminished HrQoL, as measured with both generic and disease-specific HrQoL instruments. Parents of children with narcolepsy identify impaired adaptive behavior in their children and experience high levels of stress themselves. Identifying the contributory factors, together with early intervention, are needed in order to improve the HrQoL of these children and their families.

Conflicts of interest

None.

Acknowledgments

We would like to thank all the children and their parents who gave their precious time to participate in this project. Special thanks to our co-workers Ann-Sofie Andersson, Anette Larsson, Veronica Hübinette and Anette Ekberg for their help with the data collection. This study was supported by ALF Grants, Region Västra Götaland, Ahlqvist's foundation, Region Halland and the Svenska Folkfonden.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.01.004.

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