The Association Between Family Impact and Health-Related Quality of Life of Children With Idiopathic Central Precocious Puberty

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Abstract

Background

Idiopathic central precocious puberty (ICPP) reduces patient health-related quality of life (HRQoL). The impacts of disease and treatment on families are also an important concern. This study aimed to assess the impact of ICPP on the HRQoL of children and parents; its impact on family functioning; and to determine the association between patient HRQoL and family impact, comprising the HRQoL of parents and family functioning.

Methods

We conducted a case-control study in Chongqing, China. A case group of 134 children with ICPP aged 5 to 12 years and their caregivers was recruited from a children's hospital in Chongqing. A total of 210 gender- and age-matched subjects from two schools were selected as controls. Patient HRQoL was assessed by administering the PedsQL^{TM}4.0 Generic Core Scales (GCS). Impacts of ICPP on parental HRQoL and family functioning were evaluated by the PedsQL^{TM} Family Impact Module (FIM).

Results

A total of 344 subjects were enrolled, with 134 in the case group and 210 in the control group. Children with ICPP scored lower than controls in all HRQoL domains except physical functioning. In particular, the two groups were significantly different in emotional functioning scores (77.39±17.97 vs 84.12±14.35, P<0.001). Compared with controls, ICPP families had lower scores in all dimensions of the PedsQL^{TM}4.0 FIM scale. In the case group, patient HRQoL was significantly correlated with family impact scores (r= 0.224, P<0.05), but not with the dimensions of social functioning, communication, worry, and family relationships.

Conclusions

ICPP worsens the HRQoL of patients and their parents, and also impairs family functioning. In addition, parents with higher HRQoL scores and family functioning generally reported higher HRQoL of children with ICPP. These findings suggest that health care professionals should identify and monitor ICPP patients' psychosocial problems proactively, and provide targeted interventions to reduce family impact and thereby improve patient HRQoL.

Background

Idiopathic central precocious puberty (ICPP) has become a common endocrinopathy in China, with an annual incidence of 43/10,000 population [1], which exceeds the global incidence of 1/5000 to 1/10,000 [2]. ICPP is defined as the development of secondary sexual characteristics following the activation of the hypothalamic-pituitary-gonadal axis before age 8 in girls and age 9 in boys [2] of unknown etiology after

a diagnostic evaluation. Since the mid-1980s, gonadotropin releasing hormone agonists (GnRHa) have become gold-standard treatments for ICPP, with main therapeutic goal of improving final height [3].

Currently, the medical model has shifted to a bio-psycho-social model, leading clinic staff to recognize the value of all dimensions of health that go beyond physical well-being [4, 5]. previous studies found that children with ICPP undergoing treatment may suffer persistent physical and mental health complications, and also experience adverse psychosocial outcomes that reduce HRQoL. GnRHa therapy can improve final height [6, 7], but may also result in increased body mass index [8–10]. Girls with ICPP have demonstrated significantly higher emotional reactivity, but similar cognitive and psychosocial functioning as controls [11]. Through semi-structured interviews, Baumann et al. [12] found that girls who experienced precocious puberty tended to be shy, lonely, and often feel inferior, moody, or sad. A Chinese study demonstrated body image dissatisfaction in children with ICPP that persisted after 12 months of GnRHa treatment [13]. A cross-sectional study in Korea found that children with ICPP had a more obese body image and an exaggerated sense of breast development compared to controls [14].

Parents of children with ICPP are confronted by the challenges of chronic disease management, such as prolonged illness, frequent re-examinations, and cost burdens. A qualitative study in China found that caregivers expressed anxiety and guilt when caring for children with ICPP [15]. An American study reached similar conclusions; caregivers reported anxiety and guilt while explaining the diagnosis and treatment process to their child, as well as to other family members, and also expressed a desire to affiliate with others experiencing similar struggles [16]. A study using the World Health Organization quality of life questionnaire found that parents of children with ICPP had lower scores on physical and mental health subscales than controls [17].

Although some researchers have focused on the impact of ICPP on the HRQoL of both patients and their caregivers and on family functioning, associations between patient HRQoL and family impact have heretofore undergone limited study. Consequently, the aim of this study was to assess the impact of ICPP on the HRQoL of children and their parents and on family functioning in Chongqing, China, by comparing PedsQL^{TM}4.0 Generic Core Scales (GCS) and PedsQL™ Family Impact Module (FIM) scores with those of controls, and to determine the association between patient HRQoL and family impact. Study findings could potentially provide a family-centric perspective to inform the development of clinical interventions to improve the HRQoL of children with ICPP.

Methods

Participants and setting

To achieve the power (1-β) of 0.80 under the probability of type I error (α) of 0.05, hypothetical mean scores of Psychosocial Health Summary Score were 82.0 and 87.0 in the case and control groups, respectively, with a standard deviation of 10. The sample size was determined by using the formula of $n = (\sigma((z1-\alpha/2 + z1-\beta)/(\mu A-\mu B)))2$. A minimum of 139 subjects was required for the case and control

groups, respectively. A cohort of 134 children with ICPP and their primary caregivers was recruited from a Triple A children's hospital from April to September 2019 in Chongqing by using the convenience sampling method, and 210 gender- and age-matched subjects were selected concurrently from two primary schools in Chongqing by the stratified sampling method.

The case group met the following inclusion criteria: 1) new diagnosis of ICPP, 2) previously diagnosed ICPP undergoing treatment, and 3) age of 5 to 12 years. Exclusion criteria were: 1) chronic illnesses such as asthma, kidney or heart diseases, epilepsy, or other comorbidities that influence HRQoL; 2) a history of psychological trauma such as the death of a family member; or 3) refusal of either the patient or their primary caregivers to participate. The control group met the following inclusion criteria: 1) age of 5 to 12 years, and 2) voluntary participation of the patient and their caregivers. Children with recent or past diagnoses of ICPP or who had other diseases that influence HRQoL were excluded from the control group. This study was approved by the Ethics Committee of Children's Hospital of Chongqing Medical University. All caregivers provided written informed consent.

Procedure

The investigators were trained before data collection to ensure the quality of clinical research practices. In the case group, parents completed a demographic questionnaire and the PedsQL^{TM} FIM, whereas patients completed the PedsQL^{TM}4.0 GCS at the time of diagnosis or during outpatient follow-up. In the control group, children completed the PedsQL^{TM}4.0 GCS and brought the demographic questionnaire and the PedsQL^{TM}4.0 FIM to their parents for completion, which were returned to the head teacher on the following day, and were then collected by the investigators.

Measures

Demographic variables included age, gender, weight, height; number of children in the family; and caregiver relationship (e.g., parents or grandparents). The caregivers' basic information included living environment (e.g., urban, rural), educational level (primary school, middle school, high school, or university and higher), employment status (employed, unemployed/housewives) and monthly income (<5000, 5,000-10,000, >10,000 Chinese Yuan [CNY]). Clinical characteristics of children with ICPP included whether they were newly diagnosed or already undergoing follow-up; age at diagnosis; disease duration; type of treatment (e.g., GnRHa or GnRHa combined with growth hormone); route of administration (e.g., intramuscular or subcutaneous injection); and duration of treatment.

The PedsQL^{TM} GCS questionnaire was developed by Varin et al. [18] to assess the impact of disease and treatment on pediatric patients' HRQoL during the preceding month. It consists of 23 items divided into four dimensions including physical (8 items), emotional (5 items), social (5 items) and school (5 items) functioning. A 5-point Likert scale was used to estimate problem frequencies: 0=never, 1=almost never, 2= sometimes, 3=often, 4=always. Items are then reverse scored and transformed into a scale of 0-100 (0=100, 1=75, 2=50, 3=25, 4=0), with higher scores representing better HRQoL status. The Total Summary

Score was calculated as the sum of all 23 items divided by the number of items answered. The Total Summary Score can be further divided into the subscales of Physical Health Summary Score and Psychosocial Health Summary Score. The Psychosocial Health Summary Score was computed as the sum of 15 items of emotional, social and school functioning divided by the number of items answered. This study used self-reports of the Chinese version of the PedsQL^{TM} GCS, which was cross-culturally adapted by Hao et al [19]. The instrument showed good internal consistency and reliability, with Cronbach' s alpha coefficients of 0.862 in the case group and 0.745 in the control group.

The PedsQL^{TM} FIM was developed by Varin et al [20] as a parent-reported instrument to measure the impact of pediatric chronic disease on parents' HRQoL and family functioning. The questionnaire consists of 36 items divided into 8 dimensions including physical functioning (6 items), emotional functioning (5 items), social functioning (4 items), cognitive functioning (5 items), communication (3 items), worry (5 items), daily activities (3 items), and family relationships (5 items). The former 6 dimensions measure parents' self-reported HRQoL, whereas the latter 2 dimensions measure parent-reported family functioning. Each item has five Likert response options to assess the frequency of problems: 0 (never), 1 (almost never), 2 (sometimes), 3 (often), and 4 (almost). Items are then linearly transformed to a 0-100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate lower family impact. The total score is calculated as the sum of all 36 items divided by the number of items answered. The parents' HRQoL Summary Score is calculated as the sum of the 20 items of physical, emotional, social, cognitive functioning subscales divided by the number of items answered, and the family functioning summary score is calculated as the sum of the 8 items of daily activities and family relationships subscales divided by the number of items answered. We used the Chinese version of PedsQL^{TM} FIM translated by Chen et al [21]. It has shown good internal consistency and reliability, with Cronbach' s alpha coefficients of 0.969 in the case group and 0.943 in the control group.

Statistical analyses

All data were analyzed using IBM SPSS version 25.0. Continuous and categorical variables were described as mean ± standard deviation (SD) and frequency (percentage n [%]), respectively. First, t-test and Chi-square (χ^2) test analyses were used to compare the demographic characteristics of the two groups. Second, the t-test was used to examine differences of the PedsQL^{TM} GCS and PedsQL^{TM} FIM scores between the two groups. Finally, Pearson correlation coefficients (*r* values) were calculated to explore the association between patients' HRQoL and family impact of case group. *P*-value<0.05 (two-sided) was considered statistically significant.

Results

The demographic characteristics of the case and control groups are summarized in Table 1. A total of 377 participates were enrolled. We excluded 20 participants with incomplete demographic information. A total of 344 participants were included in the final analysis, of whom 134 were in study group and 210 were controls. The mean age of the study group was 9.05 ± 1.07 years compared to 8.84 ± 1.02 years in

controls. One hundred and thirty patients (97.0%) were females, whereas 195 controls (92.9%) were females. The mean ages and sex distributions did not differ significantly between the two groups (Table 1). However, height, weight, number of children, parents' educational level, employment status, and family monthly income were significantly different between the two groups ($P < 0.05$) (Table 1).

Table 2 summarizes the clinical characteristics of the case group. Most (91.8%) were newly diagnosed, half were diagnosed at age 8 to 12 years old, and a majority (64.9%) reported a disease duration of less than one year. Most (79.9%) had received intramuscular injection, and had been treated for less than 1 year (73.1%).

Table 3 summarizes the PedsQL^{TM}4.0 GCS scores of the two groups. Children with ICPP scored significantly lower than controls in all HRQoL domains except physical functioning. In particular, the two groups were significantly different in emotional functioning scores (77.39 ± 17.97 vs 84.12 ± 14.35, $P < 0.001$).

Table 4 summarizes the PedsQL™ FIM scores of the two groups. Caregivers of ICPP patients had lower HRQoL and family functioning scores than those caring for healthy children.

Table 5 summarizes correlations between the HRQoL of children and family impact in the case group. There was a significant positive correlation between the HRQoL of children with ICPP and family impact scores ($r = 0.224$, $P < 0.05$), but not with dimensions of social functioning, communication, worry, and family relationships.

Discussion

This case-control study in Chongqing, China revealed that children with ICPP had lower HRQoL scores than controls, and suggests that the disease and its treatment have negative effects on parental HRQoL and family functioning. In particular, our study suggests that lower family impacts are associated with better HRQoL of children with ICPP.

Using the PedsQL^{TM}4.0 GCS instrument, our study revealed that children with ICPP performed worse than healthy peers in emotional functioning, social functioning, school functioning, psychosocial health summary scores, and total summary scores. Similarly, a study using an *Inventory of Subjective Life Quality Scale* found that ICPP patients had worse scores on subdomains of school life, depression, anxiety, and body satisfaction than healthy controls [22]. However, a study in Australia showed that children who experienced early puberty scored poorly only on PedsQL™ psychosocial health summary scores, but had similar scores in other dimensions as controls [23]. These discrepant results may be related to the different cultural adaptations of the instruments. The highly significant difference in the emotional functioning of the two groups can be attributed to physical changes caused by the premature development of secondary sexual characteristics. Earlier studies have supported this conclusion. Qiao XH et al., using the *Achenbach Child Behavior Checklist*, found that girls with ICPP manifested psychological and behavioral problems that included depression, withdrawal, somatization, social problems, and

delinquent and aggressive behaviors. Premature breast development may exacerbate the risk of behavioral problems [24]. Another study also found that children with ICPP were burdened by physical changes such as abnormally tall stature, and precocious breast development and menarche in girls. These may lead to self-perceptions of being different from peers, resulting in a lack of confidence and low self-concept [25]. Although physical differences that are caused by secondary sexual characteristics may be temporary, the impact on the child's self-esteem and feelings of alienation from the peer group may be significant [26]. These psychological and behavioral problems of children with ICPP may impair their social development and functioning. A qualitative research study found that children with ICPP experienced feelings of isolation and being bullied, and displayed aggressive bullying behavior [16]. In addition, children with ICPP require therapeutic injections at 4 to 5-week intervals and examinations every three months that may subsequently impede school attendance. Another potential factor is that chronic illnesses of children may lower parental expectations of academic performance. In our study, the physical functioning scores were similar in the two groups. This finding may be related to physical changes in children with ICPP that may be advantageous in physical activities such as sports, such as taller height caused by bone maturation.

Consequently, the PedsQL^{TM}4.0 GCS instrument can discriminate healthy children from ICPP patients. Further studies using the PedsQL^{TM}4.0 GCS instrument in children with ICPP are needed to improve the understanding of the impact of ICPP on patient HRQoL. Clinic staff should be attentive to the psychosocial changes of children with ICPP during medical treatment and offer crucial mental and social health interventions.

The impact of chronic diseases of children such as cancer [27], sickle cell disease [28], chronic pain [29], and functional constipation [30] on parents' HRQoL and family functioning has been demonstrated repeatedly. This study also demonstrated that caring for a child with ICPP is associated with lower parental HRQoL and impaired family functioning in all dimensions of the FIM. A study using SCL-90 measurements found that parents caring for a child with precocious puberty experienced physical discomfort [31]. Parents also expressed negative emotions and reported stressors such as medication side effects, diagnostic uncertainly, and financial costs that increased their psychological burden [15]. In addition, primary caregivers must balance the management of illness; which may require the daily administration of growth hormone injections, as well as supervision of the activities of daily life that include diet, sports, and sleep; with social activities, which may influence parents' social life. Parental HRQoL was impaired in this study. Our study also found that parents of patients had lower family functioning scores than controls. In China, older relatives including fathers may misperceive ICPP as a normal developmental process, and conclude that medical treatment is unnecessary, while mothers may advocate timely treatment for their children; consequently, family members may disagree on the child's treatment. Another probable explanation for lower HRQoL and family functioning may be that family members must sacrifice family activities to take care of their child with ICPP.

Health care professionals should provide disease-related information to parents of children with ICPP. Community hospitals and pediatric clinics could provide mental health courses to encourage parents to

express their negative feelings. A medical integration and cooperation model in endocrinology outpatient clinics also offers an effective approach to improve the ability of parents to manage chronic illnesses of their children.

Finally, we found a positive association between the HRQoL of children with ICPP and family impact, which suggests that the lower impact of illness on parents' HRQoL and family functioning, the better HRQoL of children with ICPP. Parents have an essential role in their children's personality development. Parental adverse emotional reactions, negative attitudes towards disease, and impaired family functioning may reduce patient HRQoL. Unhealthy emotions of parents can arouse emotional sensitivity and guilt in their children, and can also reduce the children's HRQoL [32] However, the dimensions of social functioning, communication, worry, and family relationships were not significantly related to patient HRQoL. A possible explanation is that parents may have been ashamed of discussing their children's condition with others; consequently, patients may not have been aware of their parents' psychological burdens. This finding indicates that health care professionals can provide targeted interventions to reduce family impact and thereby improve patient HRQoL.

However, this study had several limitations. First, the PedsQL^{TM}4.0 GCS is a general questionnaire and may lack of precision and sensitivity in assessing HRQoL of children with ICPP. However, this Chinese version of PedsQL^{TM}4.0 GCS has acceptable psychometric properties, and many researchers have used it to evaluate patients with other endocrinopathies such as obesity and short stature. Second, because our case group was recruited primarily from a triple A children's hospital in Chongqing, their HRQoL may not be representative of those of children with ICPP from other regions. However, our study found that ICPP impacts the HRQoL of both patients and their parents, as well as family function. Similar studies are needed in other regions of China.

Conclusion

We conclude that ICPP and its treatment not only reduced patient HRQoL, but also the HRQoL of parents, as well as family functioning. In addition, the HRQoL of children with ICPP was positively associated with parental HRQoL and family functioning. These findings suggest that health care professionals should identify and monitor the psychosocial problems of children with ICPP proactively, and initiate health education and mental health interventions to improve parent HRQoL and family functioning and thereby improve the HRQoL of patients with ICPP.

Abbreviations

ICPP: idiopathic central precocious puberty; HRQoL: health-related quality of life; PedsQL^{TM} GCS: PedsQL^{TM} Generic Core Scales; FIM: Family Impact Module; GnRHa: gonadotropin releasing hormone agonists; CNY: Chinese Yuan; SD: standard deviation; GH: growth hormone.

Declarations

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Authors' contributions

Study design: LSQ, LXH; guide for investigation: LQ; Data collection: CT, TF, WD, ZL; Analysis and interpretation of data: YH; First drafting of the manuscript: YH; revision for data and important content: LSQ, LXH. All authors are responsible for their work. All authors read and approved the final manuscript.

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Availability of data and materials

The data used or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The Ethics Review Board of Children's Hospital of Chongqing Medical University approved this study. Before investigation, written consents and assents were obtained from both caregivers and subjects who were willing to participate.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Demographic characteristics of 134 ICPP patients (study group) and 210 controls				
Variables	Study group（N, %）	Control group（N, %）	*t/F-value*	*P-value*
Patient characteristics	-	-	-	-
Female sex	130 (97.0)	195 (2.9)	2.710	0.100
Age(years)	9.05±1.07	8.84±1.02	1.783	0.076
Height (cm)	139.84±8.36	133.82±8.13	6.624	<0.001
Weight (kg)	34.73±8.60	30.37±7.13	5.093	<0.001
Children per family			40.970	<0.001
One-child	80（59.7）	53（25.2）		
Multiple-child	54（40.3）	157（74.8）		
Caregivers			3.731	0.053
Parents	125（93.3）	182（86.7）		
Grandparents	9（6.7）	28（13.3）		
Caregiver characteristics				
Living environment			0.037	0.847
Urban	127（94.8）	200（95.2）		
Rural	7（5.2）	10（4.8）		
Educational level			43.682	<0.001
Primary school	8（6.0）	34（16.2）		
Middle school	11（8.2）	54（25.7）		
High school	56（41.8）	87（41.4）		
University or higher	59（44.0）	35（16.7）		
Employment status			6.833	0.009
Employed	86（64.2）	162（77.1）		
Unemployed/housewives	48（35.8）	48（22.9）		
Monthly income (CNY)			62.269	<0.001
<5000	18（13.4）	83（39.5）		
5000-10 000	46（34.3）	97（46.2）		
>10 000	70（52.2）	30（14.3）		

The t-test was used to compare age, height and weight. The Chi-square (χ^2) test was used to compare other variables. CNY: Chinese Yuan.

Table 2 Clinic characteristics of case group（n=134）	
Variables	N（%）
New diagnosis/Follow-up	
New diagnosis	11（8.2）
Follow-up	123（91.8）
Age at diagnosis (years)	
5-7	45（33.6）
8-12	89（66.4）
Disease duration (years)	
<1	87（64.9）
1-2	34（25.4）
>2	13（9.7）
Type of medical treatment	
GnRHa	107（79.9）
GnRHa（GH	27（20.1）
Route of administration	
Intramuscular injection	90（67.2）
subcutaneous injection	44（32.8）
Duration of medical treatment (years)	
<1	98（73.1）
1-2	29（21.6）
>2	7（5.2）
GnRHa: gonadotropin release hormone agonist; GH: growth hormone	

Table 3 Comparison of PedsQL^{TM} 4.0 GCS scores between ICPP patients and controls

Scale	ICPP patients(n=134)	Control group(n=210)	*t-value*	*P-value*
	Mean□SD□	Mean□SD□		
Physical Health Summary Score	85.56±11.81	85.54±9.02	0.017	0.986
Psychosocial Health Summary Score	82.53±12.17	87.31±9.23	-3.892	<0.001
Emotional functioning	77.39±17.97	84.12±14.35	-3.659	<0.001
Social functioning	89.10±12.35	92.12±9.28	-2.421	0.016
School functioning	81.10±14.43	85.69±12.72	-3.100	0.002
Total Summary Score	83.28±11.22	210 86.87±7.59	-3.261	0.001

Psychosocial Health Summary Scores integrate emotional, social and school functioning scores.

Table 4 Comparison of PedsQL^{TM} FIM scores between ICPP patients and control group

	ICPP patients(n=134)	Control group(n=210)	*t-value*	*P-value*
	Mean□SD□	Mean□SD□		
Physical functioning	73.38±16.41	81.79±15.34	-4.822	<0.001
Emotional functioning	69.74±18.02	79.98±16.92	-5.338	<0.001
Social functioning	74.58±17.26	83.48±22.83	-3.862	<0.001
Cognitive functioning	72.50±18.08	77.80±18.73	-2.592	0.010
Communication	77.55±16.48	86.53±16.01	-5.012	<0.001
Worry	58.61±18.15	78.03±19.52	-9.395	<0.001
Parent HRQOL summary score	72.55±15.64	80.76±15.17	-4.836	<0.001
Daily activities	66.98±17.71	73.31±20.54	-3.034	0.003
Family relationships	74.25±17.40	79.69±18.23	-2.745	0.006
Family functioning summary score	70.62±15.95	76.50±17.35	-3.162	0.002
Total score	70.95±14.41	80.07±13.98	-5.833	<0.001

Table 5 Pearson's rank correlation coefficients of ICCP patient PedQL^{TM} 4.0 GCS and FIM scores

	Physical Health Summary Score	Psychological Health Summary Score	Total Summary Score
Physical functioning	0.221*	0.256**	0.267**
Emotional functioning	0.193*	0.245**	0.250**
Social functioning	0.162	0.147	0.162
Cognitive functioning	0.198*	0.153	0.177*
Communication	0.135	0.062	0.086
Worry	0.143	0.154	0.164
Parent HRQOL summary score	0.216*	0.222**	0.238**
Daily activities	0.143	0.249**	0.240**
Family relationships	0.081	0.139	0.134
Family functioning summary score	0.124	0.214*	0.206*
Total score	0.193*	0.213*	0.224*

* indicates *P*-values <0.05, ** indicates *P*-values<0.01.