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PREVALENCE AND CORRELATES OF ADHERENCE IN CHILDREN AND ADOLESCENTS TREATED WITH GROWTH HORMONE. A MULTICENTER ITALIAN STUDY.

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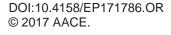
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Abstract

Objective: to evaluate the self-reported prevalence of poor adherence to rhGH therapy in a large, representative sample of Italian children and adolescents and to assess treatment and patient level correlates of poor adherence.

Methods: The study was conducted in 46 pediatric centers throughout Italy. A questionnaire was administered to consecutive children/adolescents treated with rhGH or their parents. Eligible patients were represented by subjects aged between 6 and 16 years, of both sexes, on treatment with rhGH for at least 6 months. The questionnaire was administered to the person in charge of preparing the injection. Multivariable logistic regression analysis was performed to identify factors independently associated with adherence.

Results: Overall, 1007 children/adolescents were involved, of whom 24.4% missed one or more injections during a typical week and were thus considered as non-adherent. The most frequently reported reasons for missing a dose were being away from home (33.3%), forgetfulness (24.7%), not feeling well (12.9%), and pain (10.3%).

Multivariable analysis indicated association between poor adherence and adolescence, low level of school education of parents, longer duration of treatment, need to convince the child to inject, and low level of awareness of the consequences of not following treatment properly. The likelihood of adherence markedly increased with increasing levels of perceived convenience of the device.

Conclusion: Poor adherence is still a major problem in the treatment of growth disorders. Increasing awareness and reassessment of treatment adherence on an annual basis should be part of clinical practice of pediatric endocrinologists involved with rhGH treatment.

Introduction

From 1985, the availability of the recombinant GH (rhGH) has increased the possibility of treating a larger number of children and adolescents with a wide range of different conditions, with the aim of normalizing linear growth as quickly as possible and attain a "normal adult height", whilst minimizing risks and cost [1]. The achievement of an optimal growth response during rhGH therapy is influenced by several factors such as age at treatment start, diagnosis, GH dose, duration of treatment and specifically by adherence to the prescribed GH dose [2-4]. There is no univocal definition of adherence; according to WHO, adherence is defined as the extent to which a person's behavior with regard to taking medication corresponds with agreed recommendations from a health care professional [5]. Drug adherence in pediatrics is unique because of the involvement of a third party, i.e. the parent/guardian and because the child is often unaware of the purpose of the medication and is reluctant to take it [6].Depending on the definition and methods used, suboptimal adherence to GH treatment has been reported to vary between 18% and 95% [7]. In one study, 66% of the patients had missed more than one injection per week, based on the number of GH vials returned [8]. In another study, 23% of the patients had missed more than two doses per week, based on documented GH usage versus amount prescribed [3].

Barriers to GH therapy adherence in pediatric patients may include medication factors (e.g. apparent ineffectiveness, inadequate supply and side effects), scheduling factors (social convenience), logistics of portability of the device, and cognitive/emotional problems (e.g. forgetfulness, concerns, low level of understanding of the disorder, lack of symptoms, fear of needles, poor tolerability, and inadequate family support) [7]. Additional barriers in adolescence may include denial, peer pressure and reluctance to seek medical advice [9-12]. Many of these factors have been found to be associated with poor adherence in some studies but not in others.

Starting from these premises, aim of this study was to evaluate the prevalence of non-adherence to rhGH therapy in a large, representative sample of Italian children and adolescents and to assess treatment and patient level correlates of poor adherence by the mean of a questionnaire.

Methods

The study was conducted in 46 pediatric centers, affiliated to the Italian Society for Pediatric Endocrinology and Diabetes (SIEDP/ISPED). Centers were uniformly distributed throughout Italy. In the period November 2015 –May 2016, in each center, one questionnaire per person was provided to consecutive children/adolescents treated with any rhGH or their parents. Eligible patients were represented by subjects aged between 6 and 16 years, of both sexes, on treatment with rhGH for at least 6 months.

The questionnaire was provided to the person in charge of preparing the injection, either the child/adolescent or the parent during a follow-up visit; self-reported answers by the person filling the questionnaire were then analyzed. It included 27 items, investigating demographics, type and duration of treatment, adherence (injections missed), reasons for missing an injection (more than one allowed), ease of use and reliability of the device used, satisfaction with therapy, level of understanding of the disease and of the importance of therapy, how often the parent needed to convince the child to inject (never, sometimes, often, always) (appendix 1). Pain during the injection was assessed through a visual-analogue scale, ranging from 1 (absence of pain) to 10 (severe pain). Adherence was **arbitrarily** defined as no injection missed over a typical week, while non adherence as one or more than 1 injection missed over a typical week during the last 12 months of rhGH; a "typical week" was defined as a week during school time in the last 12 months of rhGH treatment. When parents had a different level of school education, the highest level was considered. The questionnaire was self-administered during a routine follow-up visit and it was completely anonymous: no patient-specific information was requested including data on demographics, disease specificity and rhGH brand and thus no informed consent was needed.

Statistical methods

Descriptive statistics were reported in terms of absolute frequencies and percentages for

qualitative data, and the Pearson's chi-square test or Fisher's exact test, if appropriate, were applied to compare proportions. Quantitative data were described in terms of median values and inter-quartile range (IQR) values due to their non-normal (Gaussian) distribution. Accordingly, comparisons between groups were performed by the nonparametric Mann-Whitney U test.

Bivariate analysis of study variables for comparison between adherent and non- adherent subjects was applied excluding missing data.

Multivariable logistic regression analysis was performed to identify factors independently associated with adherence. Variables significantly and independently associated with adherence at bivariate analysis or possible confounders were entered in the model: age, highest level of education of the parent, duration of GH therapy, convenience of the device, how often the parent has to convince his child to inject and awareness of the consequences of not following treatment properly.

The odds ratio (OR) with the 95% confidence interval (CI) was calculated. In order to measure the global effect of each predictor on the outcome, the Likelihood-ratio test and the test for trend (considering variables as continuous) were applied.

All tests were two-tailed and a p value < 0.05 was considered statistically significant. All analyses were performed by using Stata (StataCorp. Stata Statistical Software, Release 11.0 College Station, TX, Stata Corporation, 2009).

Results

Overall, 1007children/adolescents treated with rhGH were involved. The questionnaire was filled in by 771 parents (76.6%) and 221patients (21.9%); for 15 additional questionnaires (1.5%) the person filling in the questionnaire could not be assessed.

Patient characteristics and descriptive statistics of the answers to the questionnaire are reported in table 1. All age classes were well represented. The duration of rhGH therapy exceeded 3 years in almost half of the sample, while the duration of use of the current device was over 12 months in 70.3% of participants. The injection was prepared by the parent in 76.8% of the cases. The median time for the preparation of the injection was 5 minutes (IQR 2-10) with a great variability (< 1 to 30 minutes) among subjects. One in three children/adolescents injected rhGH alone, with the

proportion increasing with the age of participants (12.8%, 25.0%, 40.9% and 52.2% for age classes 8-9, 10-11, 12-13, and 14-15, respectively; p<0.001).When the child/adolescent self-injected rhGH, a parent was always present in 45.7% of the cases, while in only 12.7% of the cases it was never present. Injection was associated with no or little pain for most of the participants (86.9%), and 60.8% of them considered important/very important having a device covering the needle while injecting. Almost one-third of the children/adolescents were reluctant in getting the injection, and parents needed to convince them, at least in some instances. The vast majority of participants felt confident regarding the dose administered, considered the device as convenient, and were satisfied with it. Also, over 90% of the participants reported a moderate to high degree of knowledge of their condition, considered rhGH therapy important, and were aware of the benefits and consequences of not following the therapy properly. The level of satisfaction with the treatment and the time dedicated to the child by the healthcare team was generally high.

Overall, 72.1% of participants reported they never missed an injection during a typical week, 22.4% missed one injection, 2.0% missed two or more injections, 3.5% did not answer to this question. A poor adherence, defined as missing at least one injection during the week, was reported by 24.4% (N=246) of participants that were further asked about the most frequent reasons for missing a dose with multiple answers being allowed. A total of 348 answers were received by the 246 non adherent subjects and the most frequently reported were being away from home (33.3%), forgetfulness (24.7%), not feeling well (12.9%), and pain (10.3%) (Figure 1).

Characteristics of children/adolescents and parents according to adherence are reported in table 2.Non adherence increased with the age of children/adolescents, although statistical significance was not reached. Adherent patients were more likely to have a parent with a high level of school education; they also showed a shorter duration of GH treatment and a shorter duration of use of the current device. Greater adherence was associated with the administration of the injection by the parent and with less pain. The level of confidence regarding the dose administered, the convenience of the device, and the overall satisfaction with it were also associated with adherence. Non-adherence was most common when the parent had to convince the child to inject, and when the importance of GH therapy and the consequences of not following it properly

were not fully understood. Finally, adherence was significantly associated with overall treatment satisfaction and with the time dedicated to the child by the healthcare team.

Multivariable analysis confirmed that several factors are associated with level of adherence (table 3). In particular, adolescents aged 14-15 years were 63% less likely than childrenaged 6-7 years to be adherent to GH therapy. The likelihood of adherence increased with the school level of the parent: children having a parent with high school degree were 1.6 fold more likely to be adherent and those with a graduated parent were about 2 fold more likely to be adherent compared to children having a parent with primary school level. Adherence decreased with increasing duration of treatment; compared to a duration of less than one year, the likelihood of adherence decreased by 50%, 73% and 61% for a treatment duration of 1-3 years, 3.1-5 years, and >5 years, respectively. The likelihood of adherence markedly increased with increasing levels of convenience of the device: perceiving the device as "very convenient" was associated with a four times greater likelihood of being adherent compared to considering the device as "not convenient at all". On the other hand, the frequent need to convince the child to inject was associated with a substantial reduction in the likelihood to be adherent. Finally, the level of awareness of the consequences of not following treatment properly was independently associated with the likelihood of poor adherence.

Discussion

The prevalence of poor adherence to GH therapy on growth has been reported in several studies [3, 8, 13, 14], but only few were large enough to allow analysis of the combined effect of different risk factors. The importance of maintaining rhGH without interruption has been emphasized by clinical practice guidelines issued by the American Association of Clinical Endocrinologists [15] and the Endocrine Society [16].One of the largest cohort reported on 217-naïve patients across six pediatric endocrinology centers showed that good adherence to therapy was associated with higher height velocity [17]. Our study involved 46 pediatric clinics and a very large number of children/adolescents treated with rhGH, representing almost one-tenth of all patients in Italy. The study showed that one in four participants missed at least one injection a week, thus confirming that poor adherence is still a major problem in the treatment of growth disorders. Poor adherence

was associated with increasing age of the children, with low levels of school education of the parents, and with a longer duration of treatment. The frequent need to convince the child to inject was also associated with a suboptimal adherence. On the other hand, perceiving the device as convenient markedly increased the likelihood of being adherent to GH therapy. Major reasons for missing a dose were reported to be scheduling issues (being away from home), forgetfulness, intercurrent illness, and pain. Some of the former factors may be improved by using long acting GH compounds which represent a novel treatment approach of growth disorders not yet commercially available (18). Thus, the impact of long acting GH treatment on adherence needs to be proven.

Comparison with current literature is made difficult by the different definitions of non-adherence adopted. In a study on 75 patients in UK, 39% had missed >1 injections per week and 24% had missed >2 injections [3]. In another study involving 175 patients in New Zealand, 34% had missed >1 injection per week [8]. In a larger study on 631 patients in North America [13], the proportion of patients missing ≥3 injections per month ranged between 15 and 24%. Overall, our data suggest a slightly better adherence to rhGH therapy in Italy, with 22.4% of participants missing one injection and 2% missing two or more injections during one week.

As for correlates of poor adherence, in agreement with previous studies we found that adolescence is associated with higher levels of non-compliance [10, 19, 20]. These findings call for education, empowerment, and support to the child and his/her family, particularly when the responsibility for managing the therapy is assigned to the adolescent.

In our study the likelihood of poor adherence decreased with increasing levels of school education of the parent. School education can be considered as a proxy of socio-economic status, and an association between low socio-economic level, low levels of education, and poor adherence to rhGH therapy has been previously documented [14, 21].Low education can also be associated with poor understanding of the disease and its treatment, thus suggesting that modalities and frequency of education and training for parents should be tailored on their specific needs and characteristics. In line with previous studies [3, 22], we also found that the likelihood of being adherent decreases as the duration of rhGH therapy increases.

The need for a long-term commitment to daily subcutaneous injections has major implications for the child and the family. Reinforcing education and motivation, providing regular feedbacks about the efficacy of the treatment, addressing specific barriers to adherence from the point of view of the child and his/her parents and eliciting their preferences can help maintain adherence during the years. In this respect, the choice of the device can play an important role and a recent study showed that injection-recording device could enhance the ability of physicians to monitor adherence [23]. In our study 17.2% of non-adherent children/adolescents vs. 8.4% of adherent ones reported pain associated with the injection. Indeed, puberty and self-administration of medication have been shown to be negative predictors of adherence to GH therapy, illustrating the importance of re-engaging with patients, parents and careers on a regular basis [24].

The frequent need to convince the child to inject represented an independent correlate of non-adherence. These findings suggest that increasing the acceptability of the device can improve adherence. On the same line, we found that one in five non-adherent participants considered not convenient the device they were using. At multivariate analysis, perception of convenience of the device was by far the most important correlate of adherence. Offering patients different options of rhGH injection devices, preferably based on personalized characteristics (indications, formulations, waste, age, socioeconomic status, simplicity) thus represents an important aspect, and restrictions of this choice for financial reasons may have negative effects on patient outcomes and potentially undermine longer-term health-economic benefits [7].

The study has limitations. First, adherence was **defined arbitrarily and was** self-reported and the real frequency of injections can have been overestimated. On the same line, the study was conducted in current users, and no information on treatment dropouts was available. Finally, perceptions of parents can differ from those of children. Nevertheless, the study provided a realistic picture of the problems faced by the person in charge of preparing the injection, being it the parent or the child/adolescent.

In conclusion although adherence to GH therapy is difficult to assess reliably, the results of our survey in a large cohort of children and adolescents show that the great majority of Italian patients treated with rhGH have a good adherence to the scheduled treatment. Target for intervention should be focused on adolescents, patients treated for longer time and those with parents with

low education. Moreover, convenience of the device appears to have an impact in order to further increase adherence to treatment. Increasing awareness and reassessment of treatment adherence should be part of clinical practice of pediatric endocrinologists involved with rhGH treatment and future studies are needed in order to correlate clinical outcomes in terms of height gain and metabolic consequences to adherence.

There is a need for multifactorial and effective interventions to improve adherence by combining risk-assessment and screening of poor adherent patients. The choice of device, training family and patients, perception of parents and patient's behavior and their support are determinant factors. Increasing awareness and reassessment of treatment adherence on an annual basis should be part of clinical practice of pediatric endocrinologists involved with rhGH treatment.

Figure1. Frequency (%) of the most frequent reasons for missing a dose of rhGH

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Table 1. Patients/parents characteristics and answers to the questionnaire (N=1007).		
Characteristic	N	%
Age of child/adolescent, n (%)		
6-7	95	9.4
8-9	135	13.4
10-11	209	20.8
12-13	216	21.5
14-15	263	26.1
Missing	89	8.8
Highest level of education of the parent, n (%)		
Primary school	221	22.0
High school	481	47.8
Graduated	286	28.4
Missing	19	1.8
Duration of GH therapy, n (%)		
6-11 months	160	15.9
1-3 years	373	37.0
3.1-5 years	231	22.9
>5 years	229	22.7
Missing	14	1.4
Duration of use of current device, n (%)		
<6 months	67	6.7
6-12 months	200	19.9
>12 months	708	70.3
Missing	32	3.2
Number of injections missed ina typical week, n(%)		
None	726	72.1
1	226	22.4
≥2	20	2.0
Missing	35	3.5
GH injection performed by, n (%)		
Parent	675	67.0
Child/adolescent	324	32.2
Missing	8	0.8
GH injection prepared by, n (%)		
Parent	773	76.8
Child/adolescent	224	22.2
Missing	10	1.0
Time for the preparation of the injection (minutes), median (IQR)	5	2-10
Pain during injection, n (%)		
No pain	445	44.2
Little pain	430	42.7
Pain	91	9.7
A lot of pain	17	1.0
Excruciating pain	6	0.6
Missing	18	1.8
Importance of having a device that covers the needle during injection, n (%)		
Not important	259	25.7
Of little importance	103	10.2
Important	278	27.6
Very important	334	33.2

Missing	33	3.3
Confident of having administered the right dose, n (%)		
Not at all	2	0.2
Uncertain	35	3.5
Confident	383	38.0
Absolutely confident	578	57.4
Missing	9	0.9
Convenience of the device, n (%)		
Not convenient at all	34	3.4
Inconvenient	115	11.4
Convenient enough	472	46.9
Very convenient	354	35.2
Missing	32	3.2
Satisfaction with the device, n (%)		
Not satisfied at all	5	0.5
Unsatisfied	23	2.3
Satisfied enough	411	40.8
Very satisfied	533	52.9
Missing	35	3.5
How often the parent has to convince his child to inject, n (%)		
Never	663	65.8
Sometimes	169	16.8
Often	88	8.7
Always	50	5.0
Missing	37	3.7
Degree of knowledge of the disease, n (%)		
None	7	0.7
Low	39	3.9
Moderate	518	51.4
High	404	40.1
Missing	39	3.9
Importance of GH therapy for the child's health, n (%)		
Not important	0	0.0
Of little importance	6	0.6
Important enough	176	17.5
Very important	791	78.6
Missing	34	3.4
Awareness of the consequences of not following treatment properly, n (%)		
Unaware	30	3.0
Little awareness	43	4.3
Aware enough	301	29.9
Fully aware	587	58.3
Missing	46	4.6
Treatment satisfaction, n (%)		
Not satisfied at all	0	0.0
Unsatisfied	16	1.6
Satisfied enough	293	29.1
Very satisfied	663	65.8
Missing	35	3.5
Satisfaction with the time dedicated to the child by healthcare team, n (%)		
Not satisfied at all	0	0.0
Unsatisfied	8	0.8

Satisfied enough	233	23.1
Very satisfied	732	72.7
Missing	34	3.4

Table 2. Probability of adherence to rhGH therapy by demographic, clinical and behavioral risk factors. Univariate analysis.

Characteristic, n(%)	Adherent N=726^	Non adherent N=246^	P value*
Age of child/adolescent			0.10
6-7	71 (10.6)	16(7.3)	
8-9	98 (14.7)	33 (15.1)	
10-11	161(24.1)	45 (20.6)	
12-13	162(24.3)	48(21.9)	
14-15	175(26.2)	77(35.1)	
Highest level of education of the parent			0.002
Primary school	139(19.4)	71(30.0)	
High school	358(50.0)	108(45.6)	
Graduated	219(30.6)	58(24.4)	
Duration of GH therapy			0.001
6-11 months	135(18.7)	22(9.0)	
1-3 years	273(37.9)	90(36.7)	
3.1-5 years	149(20.7)	73(29.8)	
>5 years	164(22.8)	60(24.5)	
Duration of use of current device			0.01
<6 months	54(7.6)	11(4.7)	
6-12 months	161(22.6)	36(15.3)	
>12 months	499(69.9)	188(80.0)	
GH injection performed by:			0.04
Parent	503(69.4)	153(62.2)	
Child/adolescent	222(30.6)	93(37.8)	
GH injection prepared by:			0.10
Parent	571(78.9)	182(74.0)	
Child/adolescent	152(21.1)	64(26.0)	
Pain during injection			0.004
No pain	335(46.7)	99(40.6)	
Little pain	318(44.3)	102(41.8)	
Pain	51(7.1)	34(13.9)	
A lot of pain	9(1.3)	8(3.3)	
Severepain	5(0.7)	1(0.4)	
Importance of having a device that covers the needle during injection			0.27
Not important	195(27.6)	60(25.1)	
Of little importance	70(9.9)	31(13.0)	
Important	189(26.7)	73(30.5)	
Very important	253(35.8)	75(31.4)	
Confident of having administered the right dose			<0.0001

Not at all	0(0.0)	2(0.8)	
Uncertain	21(2.9)	13(5.3)	
Confident	258(35.6)	113(46.1)	
Absolutely confident	446(61.5)	117(47.8)	
Convenience of the device			<0.0001
Not convenient at all	17(2.4)	17(7.1)	
Inconvenient	80(11.3)	33(13.8)	
Convenient enough	334(47.2)	123(51.5)	
Very convenient	277(39.1)	66(27.6)	
Satisfaction with the device			0.006
Not satisfied at all	5(0.7)	0(0.0)	
Unsatisfied	13(1.9)	10(4.2)	
Satisfied enough	280(39.9)	115(48.7)	
Very satisfied	404(57.6)	111(47.0)	
How often the parent has to convince his child to inject			<0.0001
Never	534(76.1)	107(45.5)	
Sometimes	100(14.3)	64(27.2)	
Often	43(6.1)	40(17.0)	
Always	25(3.6)	23(10.2)	
Degree of knowledge of the disease			0.62
None	5(0.7)	1(0.4)	
Low	25(3.6)	12(5.1)	
Moderate	366(52.4)	129(54.7)	
High	302(43.3)	94(39.8)	
Importance of GH therapy for the child's health			0.04
Not important	0(0.0)	0(0.0)	
Of little importance	3(0.4)	3(1.3)	
Important enough	116(16.5)	52(21.9)	
Very important	583(83.1)	182(76.8)	
Awareness of the consequences of not following treatment properly			0.001
Unaware	23(3.3)	7(3.0)	
Little awareness	24(3.5)	19(8.1)	
Aware enough	201(29.1)	89(37.7)	
Fully aware	443(64.1)	121(51.3)	
Treatment satisfaction			<0.0001
Not satisfied at all	0(0.0)	0(0.0)	
Unsatisfied	9(1.3)	7(2.9)	
Satisfied enough	187(26.7)	91(38.2)	
Very satisfied	504(72.0)	149(58.8)	
Satisfaction with the time dedicated to the child by healthcare team			0.007
Not satisfied at all	0(0.0)	0(0.0)	
Unsatisfied	4(0.5)	3(1.3)	
Satisfied enough	151(21.5)	72(30.5)	
Very satisfied	548(78.0)	161(68.2)	

* Chi square test or Fisher exact test
^ Missing data were excluded from analysis

Table 3. Independent variables of association with adherence: results of logistic regression analysis.		
	Odds Ratio (95% IC)	P-value
Age of child/adolescent, years	0.83 (0.72-0.95)	0.008[*]
6-7	ref.	
8-9	0.55 (0.26-1.17)	
10-11	0.82 (0.40-1.70)	0.0089[^]
12-13	0.62 (0.30-1.27)	
14-15	0.37 (0.18-0.75)	
Highest level of education of the parent	1.35 (1.06-1.72)	0.013[*]
Primary school	ref.	
High school	1.62 (1.05-2.49)	0.0216[^]
Graduated	1.92 (1.19-3.11)	
Duration of GH therapy	0.74 (0.62-0.88)	0.001[*]
6-11 months	ref.	
1-3 years	0.50 (0.26-0.94)	0.0004[^]
3.1-5 years	0.27 (0.14-0.52)	
>5 years	0.39 (0.20-0.77)	
Convenience of the device	1.44 (1.16-1.79)	0.001[*]
Not convenient at all	ref.	
Inconvenient	2.30 (0.92-5.77)	0.0098[^]
Convenient enough	2.69 (1.19-6.06)	
Very convenient	3.91 (1.69-9.05)	
How often the parent has to convince his child to inject	0.49 (0.41-0.58)	<0.001[*]
Never	ref.	
Sometimes	0.36 (0.23-0.56)	<0.001[^]
Often	0.17 (0.10-0.30)	
Always	0.16 (0.08-0.32)	
Awareness of the consequences of not following treatment properly	1.37 (1.09-1.73)	0.007[*]
Unaware	ref.	
Little awareness	0.51 (0.14-1.93)	0.0249[^]
Aware enough	0.82 (0.27-2.55)	
Fully aware	1.33 (0.43-4.06)	

[*]Test for trend
[^] Likelihood-ratio test

APPENDIX 1 -SURVEY ON ADHERENCE TO GH Therapy

Center: _____

Type: **University Center**: ☐   **Hospital Center**: ☐

Is available a dedicated nurse to GH therapy:

      Yes   ☐   No   ☐

Date of filling out questionnaire: [_][_]/[_][_]/[_][_][_][_]

DEMOGRAPHIC DATA

Region of residence: _____

Person filling-out the questionnaire:

      Parent   ☐   Child/Adolescent: ☐

Age of child/adolescent:

      A. >6 years <8 years

      B. >8 years <10 years

      C. >10 years <12 years

      D. >12 years <14 years

      E. >14 years <16 years

1. The highest qualification or level of schooling of the father:

      A. Primary school

      B. High school

      C. Graduation

      D. Other

2. The highest qualification or level of schooling of the mother:

      A. Primary school

      B. High school

      C. Graduation

      D. Other

3. For how long the child/adolescent is being treated with GH:

      A. 6 - 12 months

B. 1 - 3 years

C. > 3 years

D. >5 years

4. How long the child/adolescent has being using the current device?

A. < 6 months

B. 6 -12 months

C. >12 months

5. The GH injection is performed by the child/adolescent?

Yes ☐   No ☐

6. If Yes, is the parent always present to control that the GH injection is being correctly performed?

A. Yes, 7 days/7 days

B. Yes, ≥5 days /7 days

C. Not always, <5 days /7 days

D. Never

7. Who is in charge of preparing the GH injection?

A. Parent   *B. Child/adolescent*

8. How long does it takes the preparation of the GH injection?

_____*Minutes*

(Please consider also the time needed before the preparation, after having retrieved the drug from the fridge)

9. Does it happen in a typical week during the last 12 months of GH therapy to miss an injection?

A. Never

B. Yes, once a week

C. Yes, twice a week

D. Yes, more than twice a week

10. For what reasons the child/adolescent might miss *a* GH injection in a typical week?
(number the reasons from 1-7 in order of importance: 1 is the most important)

[_] Forgetfulness

[_] Forgot to renew the prescription

[_] Pain during injection

[_] Not feeling well

[_] Away from home

[_] No fridge available

[_] Malfunctioning of the device

11. How do you define the level of pain that the child feels during the GH injection? (on a VAS scale)

1	2	3	4	5	6	7	8	9	10

No pain   Little pain   Pain   A lot of pain   Excruciating pain

12. How important it is for the parent or his child to have a device that would cover the needle during the GH injection?

    A. Not important

    B. Of little importance

    C. Important

    D. Very important

13. The child/parent feels confident of having administered the right dose?

    A. Not at all

    B. Uncertain

    C. Confident

    D. Absolutely confident

14. How much does the parent believe that the device that is now using the child is convenient to be taken outside?

    A. Not convenient at all

    B. Inconvenient

    C. Convenient enough

    D. Very convenient

15. Overall, how much is the parent satisfied with the device now being used by the child?

    A. Not satisfied at all

    B. Unsatisfied

    C. Satisfied enough

    D. Very satisfied

16. How often the parent has to convince the child to have the injection?

    A. Never: 0/7 days

    B. Sometimes,: <5 /7 days

    C. Often: , ≥5 /7 days

    D. Always, 7 /7 days

17. How much is in your opinion the degree of knowledge about the child's disease?

    A. None

    B. Low

    C. Moderate

    D. High

18. How much does the parent believes that the GH therapy is important for the child's health?

    A. Not important

    B. Of little importance

    C. Important enough

    D. Very important

19.How much the parent is aware of the consequences of NOT properly following the prescribed schedule?

    A. Unaware

    B. Little awareness

    C. Aware enough

    D. Fully aware

20. Overall, is the parent satisfied with the prescribed therapy?

    A. Not satisfied at all

    B. Unsatisfied

    C. Satisfied enough

    D. Very satisfied

21. How much the parent is satisfied with the time that the medical team usually dedicate to him/her and to the child?

    A. Not satisfied at all

B. Unsatisfied

C. Satisfied enough

D. Very satisfied