Dermatology

Research Article

Dermatology 2024;240:216–225
DOI: 10.1159/000536144

Received: September 24, 2022
Accepted: January 3, 2024
Published online: January 16, 2024

Mental Health of School-Aged Children Treated with Propranolol or Atenolol for Infantile Hemangioma and Their Parents

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Keywords
Vascular tissue neoplasms · Adrenergic beta-antagonists · Long-term adverse effects · Psychosocial functioning · Parenting

Abstract
Background: Infants with infantile hemangioma (IH) have been effectively treated with propranolol or atenolol. Concerns were raised about the mental health of these

The trial registration: Netherlands Trial Register Trial NL7703.

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children at school age, due to central nervous system effects of propranolol and visible nature of IH. ***Objective:*** This study aimed to compare the mental health at school age of children treated with propranolol to children treated with atenolol for IHs and their parents. ***Methods:*** This two-centered cross-sectional study included children aged ≥6 years and treated with either propranolol or atenolol for IH during infancy. Children's outcomes were performance-based affect recognition (Dutch version of the Developmental Neuropsychological Assessment-II [NEPSY-II-NL]), parent-reported emotional and behavioral functioning (Child Behavioral Checklist [CBCL]), and health-related quality of life (KIDSCREEN-27). Parents' outcome was parenting stress (Parenting Stress Questionnaire [OBVL]). ***Results:*** Data of 105 children (36 propranolol, 69 atenolol; 6.0–11.8 years) were analyzed. Mental health outcomes did not differ between both β-blocker groups. Although overall functioning was in line with norms, children presented specific problems concerning affect recognition, parent-reported attention, and social quality of life. Parents showed increased physical symptoms, depressive symptoms, and parent-child relationship problems. ***Conclusion:*** No difference in mental health at school age was found between children treated with propranolol or atenolol for IH. Although few overall mental health problems were found, specific problems require follow-up. Follow-up of children should be directed toward affect recognition, attention, and social functioning in daily life. Problems reported by parents could be ameliorated by mental health support during and after their infant's β-blocker treatment.

Introduction

Infantile hemangioma (IH) is the most common tumor of infancy, with incidences ranging from 2.0% to 4.5% [1–3]. Up to 38% of IHs require treatment to minimize complications like functional impairment, disfigurement, or ulceration. Propranolol, a lipophilic nonselective β-blocker, has been first-choice treatment since 2008 [4, 5]. However, reported side effects include central nervous system (CNS) effects (e.g., sleep disturbances in infants, impaired affect recognition in healthy adults), pulmonary effects (e.g., bronchospasm in infants), hypoglycemia, and hyperkalemia [6, 7]. Atenolol, a hydrophilic β1-selective β-blocker, is as effective as propranolol but induces fewer side effects in infants with IH, likely due to reduced blood-brain barrier passage and pulmonary effects [8–12].

Prolonged exposure to CNS effects and pulmonary effects during infancy may interfere with neurocognitive development [6, 13, 14]. Resulting problems with complex neurocognitive functions may not be visible at an early age, but subtle functional deficiencies and related mental health problems may become detectable at school age as social interactions become increasingly complex [15, 16]. Previous follow-up of seven-year-old children who were treated with propranolol for IHs did not find any mental health problems but was limited by a small sample size (n = 27) [17].

Despite treatment, up to 86% of IHs result in visible sequelae, like fibrofatty tissue, telangiectasia, and anetodermic skin [18, 19]. The visibility of IHs may also affect the mental health of children and their family [20]. During infancy, IHs burden parental quality of life and family life, especially when located in the facial area [21–23]. Parents of infants with IHs report social stigma, emotional difficulties, and behavioral changes, such as avoiding to take their child out in public [24, 25]. Additionally, some parents worry about future mental health difficulties of their child. Specifically, parents raise concerns about social stigma, teasing, and bullying due to visible residual IH lesion [26, 27].

These concerns are in line with the psychological comorbidity of school-aged children with other visible medical conditions [28–30]. Nonetheless, previous studies of school-aged children with IHs did not detect emotional and behavioral problems or a decreased quality of life [31–33]. However, some studies included both IHs with and without complications, which may have led to an underestimation of mental health problems as IHs with complications could leave more visible residual lesions [18, 34].

This study aimed to investigate the mental health of school-aged children (age ≥6 years old) who were treated during infancy (age ≤12 months old) with propranolol or atenolol for IH and their parents (i.e., affect recognition, emotional and behavioral problems, health-related quality of life [HRQoL], and parenting stress). Given the side-effect profiles mentioned above, we expected increased mental health problems in children treated with propranolol compared to children treated with atenolol. Additionally, we compared scores of all children to norm scores based on the general Dutch population and explored parents' perceptions of visibility and specific concerns, like bullying and behavioral changes due to the IHs.

Methods

Participants and Design

This two-centered cross-sectional study was part of a long-term follow-up of children treated with propranolol or atenolol for IH. Detailed methods are described in Hermans et al. [35]. We screened records of all patients treated for IH at the Erasmus MC, University Medical Center Rotterdam, the Netherlands, or the

University Medical Center Utrecht, the Netherlands, between 2008 and 2014. Eligible children were ≥6 years old upon participation, had IH, and were previously treated with either ≥2 mg/kg/day oral propranolol or ≥1 mg/kg/day oral atenolol. Minimum treatment duration was 6 months, and maximum age at treatment initiation was 1 year. Recruitment took place between April and December 2019. The last recruited child was assessed in February 2020. Parents completed paper psychological questionnaires, while children participated in the neuropsychological assessment. One certified psychologist (M.M.H.) performed all assessments and was blind to the type of β-blocker treatment the child had received during infancy.

Measurements

All measures of mental health are currently used in Dutch clinical practice and accompanied with robust norm scores based on the general Dutch population with sufficient psychometric properties [36–39].

Performance-Based Affect Recognition

Children were tested on their ability to recognize emotions from photographs of other children's faces, using the Affect Recognition subtest of the Dutch version of the Developmental Neuropsychological Assessment-II (NEPSY-II-NL). Total scores were compared to norms and converted into age-corrected percentiles. Percentiles ≤10 were considered in the clinical (problem) range [39].

Emotional and Behavioral Problems

The Child Behavioral Checklist (CBCL) was completed by parents to assess the child's emotional and behavioral problems. This questionnaire constitutes eight syndrome scales: Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints (combined into Internalizing Problems); Rule-Breaking Behavior and Aggressive Behavior (combined into Externalizing Problems); and Social Problems, Thought Problems, and Attention Problems. All scales combined measure total problems. Higher scores indicate more problems. Raw scores were used to determine differences between β-blocker groups and deviances from norms. Age- and sex-corrected T-scores (mean: 50, standard deviation: 10) were used to determine scores within the (sub)clinical range (percentile ≥93) [36].

Health-Related Quality of Life

The KIDSCREEN-27 was completed by parents to assess the child's HRQoL in the following areas: Physical Well-Being, Psychological Well-Being, Autonomy and Parent Relation, Social Support and Peers, and School Environment. This resulted in T-scores (mean: 50, standard deviation: 10). Higher scores indicate better HRQoL [37].

Parenting Stress

The Parenting Stress Questionnaire (Dutch: *Opvoedingsbelastingvragenlijst* [OBVL]: "Burden of parenting") was used to assess parents' concerns about parenting. The Total Score involved five subscales: Parent-Child Relationship Problems, Parenting Problems, Depressive Mood (parent), Parental Role Restriction, and Physical Problems (parent). Age-corrected T-scores (mean: 50, standard deviation: 10) were used to determine scores within the clinical range (percentile ≥91). Higher scores indicate more parenting stress [38].

Additionally, parents were surveyed about specific concerns related to the IHs. Subjective visibility was rated by parents as described by Van Dalen et al. [40]. Questions about bullying and about parents' worries regarding their child's future were adapted from Feragen et al. [41]. Parents were given the opportunity to comment on their responses. Location of the IHs, cumulative β-blocker dosage, treatment duration, and the child's age at β-blocker treatment initiation were obtained from patient records. Mother's educational level was used for its association with socioeconomic status, and parent intelligence was classified according to the International Standard Classification of Education (ISCED) guidelines [42].

Data Analysis

Differences between the β-blocker groups were analyzed with Mann-Whitney U-tests (for continuous variables) or Fisher exact tests (for dichotomous variables). Multivariable linear regression (for continuous variables) or logistic linear regression (for dichotomous variables) was performed to correct for child's age, child's sex, mother's education, cumulative dose, treatment duration, and age at treatment initiation.

Differences between children treated with β-blockers and population norms were analyzed using one-sample Wilcoxon signed rank tests (for continuous variables) or χ^2 tests (for dichotomous variables). The CBCL was also analyzed with a multivariable linear regression to correct for child's age and sex, using original Dutch norm data which we obtained from the authors [36].

As missing data were rare (<5% of data), complete case analysis was used. To account for multiple comparisons, we performed a Dunn-Šidák correction over a two-sided $p < 0.05$, separately within each mental health questionnaire (i.e., CBCL, KIDSCREEN-27, and OBVL). Effect sizes were calculated and interpreted according to Cohen's guidelines [43].

Results

Overall, 299 children were screened for eligibility. Out of 158 eligible children, 105 (66%) participated. A total of 36 children had been treated with propranolol and 69 children with atenolol [35].

Table 1 shows the participant characteristics. Most children were female (81%) and had IHs located in the head and neck area (80%). Compared to children treated with propranolol, children treated with atenolol were significantly younger ($p < 0.001$), more often had IHs located in the head and neck area ($p = 0.020$), had a shorter treatment duration ($p = 0.001$), and had received a lower cumulative β-blocker dosage ($p < 0.001$).

Comparison between Propranolol and Atenolol

Children treated with propranolol or atenolol and their parents did not differ on any of the mental health measures (i.e., NEPSY-II-NL Affect Recognition, CBCL, OBVL, KIDSCREEN), both in uncorrected analyses and analyses corrected for child age and sex, maternal education, cumulative dose, treatment duration, and age at treatment initiation (online suppl. Table S1–S4; for all online suppl. material, see https://doi.org/10.1159/000536144).

Table 1. Participant characteristics

	All (n = 105)	Propranolol (n = 36)	Atenolol (n = 69)	p value
Demographics				
Child age, years				
Median (IQR)	7.4 (6.7–8.5)	8.0 (7.3–8.8)	7.1 (6.4–8.1)	<0.001
Range	6.0–11.8	6.4–11.8	6.0–9.7	
Child sex, n (%)				
Female	85 (81)	29 (81)	56 (81)	>0.99
Male	20 (19)	7 (19)	13 (19)	
Education mother, n (%)				
Low	14 (13)	6 (17)	8 (12)	0.89
Average	28 (27)	8 (22)	20 (29)	
High	62 (59)	22 (61)	40 (58)	
Unknown	1 (1)	0 (0)	1 (1)	
Clinical information				
Location of IH[1], n (%)				
Head and neck	84 (80)	24 (67)	60 (87)	0.02
Trunk	13 (12)	6 (17)	7 (10)	0.36
Genital area	13 (12)	7 (19)	6 (9)	0.13
Extremities	7 (7)	3 (8)	4 (6)	0.69
Age at treatment initiation, months				
Median (IQR)	3.5 (2.2–5.1)	3.6 (2.2–5.3)	3.4 (2.2–5.0)	0.58
Range	0.92–11.4	1.64–11.4	0.92–10.9	
Treatment duration, months				
Median (IQR)	13.8 (10.9–19.4)	18.6 (12.5–22.7)	13.0 (10.4–15.8)	0.001
Range	6.41–62.7	9.13–62.7	6.41–56.8	
Cumulative dose, mg/kg				
Median (IQR)	577.4 (387.2–881.7)	1,122.7 (718.6–1,282.3)	418.7 (310.0–619.7)	<0.001
Range	186.6–3,544	494.1–3,544	186.6–2,206	

Table adapted from Hermans et al. [35]. p values indicate differences in participant characteristics between propranolol and atenolol groups. Continuous variables were not normally distributed and were analyzed with a Mann-Whitney U test. Dichotomous variables were analyzed with a Fisher's exact test. [1]A total of 105 patients had a total of 128 IHs. The variable "location of IH" represents the number of children with at least one IH in each region.

Comparison between β-Blockers and Norms

Children's performance on NEPSY Affect Recognition was significantly worse than norms. In total, 45% of the children (n = 47) scored within the clinical range (percentile ≤10), as opposed to 10% of children in the norm group (p < 0.001). This corresponded to a large effect size (φ = 1.16).

Compared to norms, parents reported significantly more problems on the CBCL syndrome scale Attention Problems, although the effect size was small (Table 2). Scores on other CBCL syndrome scales and the broadband scales (Internalizing Problems, Externalizing Problems, and Total Problems) did not differ from norms.

Parent-reported KIDSCREEN-27 scores were significantly lower in the area of social support and peers (Table 3). In contrast, scores on KIDSCREEN-27 scales Autonomy and Parent Relation and School Environment were higher than norms. Other KIDSCREEN-27 scale scores did not differ from norms.

Scores of OBVL scales Parent-Child Relationship Problems, parent's Depressive Mood, and parent's Physical Health Problems were significantly higher than norms; effect sizes were medium to large (Table 4). Other scales and the OBVL Total Score did not significantly differ from norms.

Domains of Concerns Related to the IH

More than half of all parents indicated that their child's IH was not visible at all (n = 63, 60%; Table 5). Furthermore, 76% (n = 80) of parents did not experience that bystanders looked at their child's IH. Two parents (2%) indicated their child avoided situations because of the IH. Specifically, one child covered IH located on the face with hair; another child covered IH located on the trunk with a swimsuit. According to parents, 12 children (11%) had

Table 2. Analyses of the difference in emotional and behavioral problems between children treated with β-blockers for IH and children from the general population (Child Behavior Checklist 6–18)

Child Behavior Checklist 6–18 scale	Descriptives				Univariate comparison of raw scores		Multivariate comparison of raw scores[1]		
	participants (n = 104)		general population (n = 764)		p value	Pearson's r	B (95% CI)	p value	Cohen's f^2
	raw score, mdn (IQR)	(sub) clinical, n (%)	raw score, mdn (IQR)	(sub) clinical, %					
Syndrome scales									
Anxious/Depressed	2 (1–5)	11 (11)	2 (1–5)	7	0.58	0.02	−0.1 (−0.8 to 0.6)	0.74	0.00
Withdrawn/ Depressed	1 (0–2)	8 (8)	1 (0–3)	7	0.39	0.03	−0.1 (−0.5 to 0.4)	0.76	0.00
Somatic Complaints	1 (0–3)	8 (8)	1 (0–2)	7	0.07	0.06	0.2 (−0.2 to 0.6)	0.40	0.00
Social Problems	2 (1–4)	7 (7)	2 (1–4)	7	0.75	0.01	0.3 (−0.2 to 0.9)	0.24	0.00
Thought Problems	2 (1–4)	22 (21)	2 (0–3)	7	0.033	0.07	0.7 (0.2–1.2)	0.009	0.01
Attention Problems	4 (2–7)	18 (17)	3 (1–6)	7	0.10	0.06	1.3 (0.6–2.0)	0.001	0.01
Rule-Breaking Behavior	1 (0–2)	9 (9)	1 (0–2)	7	0.53	0.02	0.1 (−0.3 to 0.5)	0.68	0.00
Aggressive Behavior	4 (1–6)	10 (10)	4 (2–7)	7	0.56	0.02	0.6 (−0.5 to 1.6)	0.29	0.00
Broadband scales									
Internalizing Problems	5 (3–9)	18 (17)	5 (2–9)	15	0.99	0.00	0.0 (−1.2 to 1.2)	0.99	0.00
Externalizing Problems	5 (2–8)	15 (14)	5 (2–9)	15	0.57	0.02	0.6 (−0.7 to 1.9)	0.34	0.00
Total Score	23 (13–35)	22 (21)	22 (13–35)	15	0.85	0.01	2.9 (−1.0 to 6.7)	0.15	0.00

Higher scores indicate more problems. $p < 0.005$ is considered statistically significant for secondary outcome analyses (Dunn-Šidák correction). Effect size Pearson's r: small = 0.1, medium = 0.3, large = 0.5. Effect size f^2: small = 0.02, medium = 0.15, large = 0.35 [43]. [1]Corrected for child's age, child's sex, and mother's education.

experienced negative comments or bullying due to IH at some point in their lives. Seventeen parents (16%) reported being worried about their child's future. Nine of these parents commented they were concerned about the consequences of the residual lesion during puberty and its effect on body image.

Discussion

This study evaluated the mental health of school-aged children who were treated with propranolol or atenolol for IH during infancy and their parents. Mental health was thoroughly assessed with a performance-based measure of affect recognition and parent reports of the child's emotional and behavioral problems, the child's HRQoL, and parenting stress.

The primary hypothesis was that children treated with atenolol would have fewer mental health problems at school age, given that atenolol treatment is as effective as propranolol treatment but associated with fewer side effects [8–12]. Contrary to this hypothesis, the β-blocker groups did not differ on any of the mental health measures. These findings add to our previous results, which suggested that long-term cognitive functioning, physical health and development, and the esthetic outcome of the

Table 3. Analyses of the difference in HRQoL between children treated with β-blockers for IH and normed scores based on the general Dutch population (KIDSCREEN-27)

KIDSCREEN-27 scale	Descriptive statistics (T-score), mdn (IQR)		Univariate comparison of T-scores	
	participants (n = 104)	reference group[1]	p value	Pearson's r
Physical Well-Being	56 (50–64)	52.68 (46.50–59.38)	0.055	0.23
Mental Well-Being[2]	53 (47–56)	52.38 (46.67–55.67)	0.74	0.02
Autonomy and Parent Relation[3]	51 (48–56)	49.10 (43.79–56.01)	<0.001	0.42
Social Support and Peers	47 (47–50)	52.59 (45.94–56.13)	<0.001	0.68
School Environment[4]	54 (51–65)	51.42 (47.69–59.34)	<0.001	0.51

Lower scores indicate more problems. $p < 0.01$ is considered statistically significant for secondary outcome analyses (Dunn-Šidák correction). Effect size Pearson's r: small = 0.1, medium = 0.3, large = 0.5 [43]. [1]Consisting of 5,142–5,367 children aged 8–11 years as described in the KIDSCREEN manual [37]. [2]One missing in the atenolol group, n = 103 (propranolol: n = 36, atenolol: n = 67). [3]Nine missing values, 3 in the propranolol group and 6 in the atenolol group, n = 95 (propranolol: n = 33, atenolol: n = 62). [4]Two missing values, 1 in the propranolol group and 1 in the atenolol group, n = 102 (propranolol: n = 35, atenolol: n = 67).

Table 4. Analyses of the difference in parenting stress between children treated with β-blockers for IH and normed scores based on the general Dutch population (Parenting Stress Questionnaire [OBVL])

Parenting Stress Questionnaire scale	Descriptives				Univariate comparison of T- scores	
	participants (n = 103)		general population (n = 764)		p value	Pearson's r
	T-score, mdn (IQR)	(sub)clinical, n (%)	T-score, mdn	(sub)clinical, n		
Parent-Child Relationship Problems	51 (45–56)	18 (18)	50	15	0.003	0.29
Parenting Problems	50 (44–62)	27 (16)	50	15	0.84	0.02
Depressive Mood (parent)	50 (46–60)	26 (25)	50	15	0.001	0.34
Parental Role Restriction	52 (46–60)	28 (27)	50	15	0.020	0.23
Physical Health Problems (parent)	56 (51–61)	26 (25)	50	15	<0.001	0.67
Total Score	50 (44–58)	22 (21)	50	15	0.49	0.07

Higher scores indicate more problems. $p < 0.009$ is considered statistically significant for secondary outcome analyses (Dunn-Šidák correction). Effect size Pearson's r: small = 0.1, medium = 0.3, large = 0.5 [43].

IH did not differ between both β-blocker groups [19, 35, 44]. Altogether, we found no indication that propranolol and atenolol have differential effects on IH involution and infant CNS development.

Nevertheless, a couple areas of concern emerged even after correction for multiple comparisons. Overall, 45% of children treated with β-blockers showed problems in effect recognition, as opposed to 10% of children in the norm group. This suggests that β-blocker use during infancy may negatively impact development of long-term affect recognition. An immediate negative effect of β-blocker use on affect recognition has been established in healthy adults [7]. Affect recognition skills are critical to social functioning, and deficits are associated with psychiatric problems throughout life, including anxiety, depression, or conduct disorder [16, 45–47].

Parents reported few emotional and behavioral problems in their children, which is in line with previous studies in children with IH [17, 40]. Nonetheless, specific problems emerged. For instance, parents reported more attention problems. This is in line with our hypothesis that children treated with β-blockers for IH during infancy may be at a

Table 5. Questions about specific domains of concerns related to the IH

Hemangioma-specific question	Response	*n* (%)
To what extent do you think your child's IH is visible?[1]	Not at all	63 (60)
	A little	23 (22)
	A fair amount	13 (12)
	Quite much	2 (2)
	Very much	3 (3)
To what extent do you experience that bystanders look at your child's IH?[1]	Not at all	80 (76)
	A little	12 (11)
	A fair amount	6 (6)
	Quite much	4 (4)
	Very much	2 (2)
Have any other children ever commented or bullied your child because of the IH?[2]	Yes	12 (11)
	No	89 (85)
	Missing	4 (4)
Do you or does your child currently avoid certain situations because your child has an IH?[3]	Yes	2 (2)
	No	100 (95)
	Missing	3 (3)
Do you have any worries about your child's future?[2]	Yes	17 (16)
	No	86 (82)
	Missing	2 (2)

[1]Question was adapted from van Dalen et al. [40]. [2]Question was adapted from Feragen et al. [41]. [3]Question was based on qualitative reports of behavioral changes in parents of children with proliferating IH [24, 25].

risk of developing attention problems due to the direct effect of β-blockers on the development of attention [35]. Although our previous performance-based evaluation of attention did not indicate deviation from population norms, parent reports may reflect neurocognitive functioning in daily life over a longer time span and therefore have greater ecological validity [35, 48, 49]. Hence, we cannot ignore possible effects of β-blocker treatment during infancy on attention functioning at school age.

According to parents, the overall HRQoL of children treated with β-blockers was good. This is in line with previous studies [27, 31, 50]. Only quality of life in the area of Social Support and Peers was reduced. Correspondingly, a previous study found that children with IH may experience social difficulties, particularly in making new contacts [32]. Parent-reported social quality of life was not impaired in that study; however, treatment type was not considered. Although HRQoL is multifaceted, children treated with β-blockers for IH may experience possible effects of β-blocker treatment, like deficits in effect recognition. Additionally, for some children, having a visible condition may impact mental health, as qualitatively reported by parents in our study.

Total scores of parenting stress did not deviate from norms. A previous study also found that parents of children with IH (up to 12 years of age) showed less total parenting stress and average levels of depression compared to norms [51]. Yet, composite scores may not reflect more subtle problems. Looking closer, significant problems were found regarding the parent-child relationship, parents' depressive mood, and parents' physical health. Possibly, parents still suffer from the intense experiences related to having an infant with IH. Parents of infants with proliferating IH report a high burden of disease, elevated parenting stress, and decreased quality of life [21, 22, 25, 52]. They have to cope with difficulties of having an infant with a medical condition and may face negative responses from bystanders to the visible difference of their infant. Bystander messages of blame and dismissal may stay with parents for a long time [53]. Yet, despite this burden, few parents are offered psychological support [21].

Due to the lack of a control group of untreated children with IH with complications, we are unable to recognize whether the aforementioned problems are attributable to the β-blocker treatment, the visible nature of the IH, or another underlying mechanism leading to both IH and functional deficits (e.g., a genetic predisposition). This

limitation should be addressed in further research. It seems that visibility is not the main concern for this patient group at school age as the majority of parents indicated that the IHs were not visible at all and few children tried to cover up the IH [19]. Furthermore, previous studies showed that subjective visibility (parent-reported) or physical location of IH is not related to emotional and behavioral problems or quality of life in school-aged children [32, 40]. Nonetheless, clinicians should remain vigilant for specific cases that do experience negative effects due to the visible nature of the IH. Furthermore, the amount of stigma experienced by children with facial differences increases with age and adolescents with visible differences show significant symptoms of anxiety, and the impact of visible residual lesion may become more prominent during adolescence [20, 29]. This was also a concern of some parents in the current study.

To conclude, no difference in mental health at school age was found between children treated with propranolol or atenolol for IH. Nonetheless, some specific problems were identified. Children's affect recognition skills, parent-rated attention problems, and social functioning should be closely monitored. Furthermore, clinical practice should be attentive toward cases that do experience negative consequences due to visible sequelae. This way, the consequences of deficits on daily functioning can be recognized and addressed in treatment or guidance.

Key Message

Independent of the β-blocker type, having IH treated with β-blockers may negatively impact mental health.

Statement of Ethics

This study was reviewed and considered exempt from the Dutch Medical Research Involving Human Subjects Act according to the Institutional Review Boards of Erasmus MC (MEC-2019-0268) and UMCU (19-115/C). All parent(s)/legal guardian(s) provided written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Funding Sources

This investigator-initiated study was supported by an unrestricted grant provided by Pierre Fabre Dermatologie.

Author Contributions

Mireille M. Hermans contributed to the study design, coordinated data collection, collected the data of the neuropsychological assessment, carried out the data analyses, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. André B. Rietman and Dr. Renske Schappin conceptualized the study and contributed to the study design, supervised data collection, carried out the data analyses, contributed to the interpretation of the results, and reviewed and revised the manuscript. Dr. Peter C.J. de Laat, Dr. Johannes M.P.J. Breur, Dr. Marlies de Graaf, Dr. Martine F. Raphael, and Prof. Suzanne G.M.A. Pasmans conceptualized the study and contributed to the study design, collected the data of the physical and dermatological assessment, contributed to the interpretation of the results, and reviewed and revised the manuscript. Dr. Jolanda M.E. Okkerse, Elodie J. Mendels, Dr. Hester R. Langeveld, prof. Saskia N. de Wildt, and prof. Corstiaan C. Breugem contributed to the study design and the interpretation of the results and reviewed and revised the manuscript. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data Availability Statement

Due to European privacy regulations (General Data Protection Regulation [GDPR]), individual participant data cannot be made publicly available online. Therefore, anonymous participant data and a data dictionary defining each field in the set will be made available upon individual request to the authors. Additional documents are available online (e.g., study protocol, https://www.trialregister.nl/trial/7703) or available upon request (e.g., informed consent forms in Dutch language).

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