

RESEARCH

Acquired hypothalamic dysfunction in childhood: 'what do patients need?' – an Endo-ERN survey

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Abstract

Objective: Hypothalamic dysfunction is a rare condition and can be encountered in patients who have been diagnosed or treated for a suprasellar brain tumor. Due to its rarity, the signs and symptoms of hypothalamic dysfunction may be difficult to recognize, leading to delayed diagnosis of the suprasellar brain tumor or to difficulties in finding the health-care expertise for hypothalamic dysfunction after tumor treatment. To improve the care and outcome of patients with acquired hypothalamic dysfunction, professionals are required to understand the patient's needs.

Design: A worldwide online survey was distributed from April 2022 to October 2022 to patients with childhood-onset hypothalamic dysfunction (as reported by the patient) following a brain tumor.

Methods: Patients were notified about the survey through patient advocacy groups, the SIOPe craniopharyngioma working group and the Endo-ERN platform.

Results: In total, 353 patients with hypothalamic dysfunction following craniopharyngioma (82.2%), low-grade glioma (3.1%) or a pituitary tumor (8.2%) or caregivers responded to the survey. Sixty-two percent had panhypopituitarism. Obesity (50.7%) and fatigue (48.2%) were considered the most important health problems. Unmet needs were reported for help with diet, exercise and psychosocial issues. Patients' suggestions for future research include new treatments for hypothalamic obesity and alternative ways for hormone administration.

Conclusions: According to the patient's perspective, care for acquired hypothalamic dysfunction can be improved if delivered by experts with a holistic view of the patient in a multidisciplinary setting with a focus on quality of life. Future care and research on hypothalamic dysfunction must integrate the patients' unmet needs.

Significance statement: Patients with hypothalamic dysfunction may experience a variety of symptoms, which are not always adequately recognized or addressed. In previous papers, the perspective of caregivers of children with craniopharyngioma has been reported (Klages *et al.* 2022, Craven *et al.* 2022). Now we address the patients' perspective on acquired hypothalamic dysfunction using an Endo-ERN global survey. According to the

Key Words

- ▶ hypothalamic dysfunction
- ▶ suprasellar brain tumors
- ▶ patient perspective
- ▶ childhood
- ▶ early onset

patients' perspective, care can be improved, with needs for improvement in the domains of obesity, fatigue and lifestyle. Research may focus on ways to improve hypothalamic obesity and alternative ways for hormone administration. Ideally, care should be delivered by doctors who have a holistic view of the patient in a multidisciplinary expert team. The results of this study can be used to formulate best practices for clinical care and to design future research proposals.

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Introduction

The hypothalamus is a key organ centrally located in the brain, linking the endocrine and the nervous systems, thereby being responsible for the homeostasis of the body. Impaired function of the hypothalamus, described as hypothalamic dysfunction (HD), can be acquired in childhood or later on due to (treatment of) suprasellar brain tumors (1). Treatment modalities for suprasellar brain tumors may include neurosurgery, chemotherapy, radiotherapy or a combination of them (2, 3). Craniopharyngioma is the most common suprasellar tumor to result in HD; however, HD is also encountered following the diagnosis and treatment of suprasellar low-grade glioma (LGG) and less frequent genetic causes (1, 4, 5).

HD following treatment for a brain tumor is a rare disease and patients may encounter difficulties in receiving optimal health care. Delay in recognition of signs and symptoms, difficulties in timely referral or assigning the correct treatment may occur. HD can have detrimental effects on the quality of life. Patients with HD may experience disturbed hunger-satiety and thirst feelings, decreased energy expenditure, behavioral problems, disturbed circadian rhythm, temperature dysregulation and pituitary dysfunction, including arginine vasopressin deficiency (diabetes insipidus (DI)) with adipsia (6, 7, 8, 9). Disturbed hunger and satiety feelings in combination with decreased energy expenditure can result in morbid obesity, with the clinical picture being very heterogeneous between patients (10, 11). Children with suprasellar tumors are more prone to develop HD than adults (12). Chronic fatigue and sleep disorders may both impact school performance and bonding with peers (13). Since children are still under development and face difficulties regarding important life events, such as finishing school, starting a career and a family, in comparison with adults that already reached those milestones, the quality of life is especially impacted in children (1).

Unfortunately, there is no effective treatment for all aspects of HD, and HD may not be the same for

every individual; some patients will experience obesity, sleep problems and panhypopituitarism while others may be more disturbed by hypothermia and DI with adipsia. Most patients with HD have accompanying pituitary insufficiency for which hormonal substitution therapy is given, often in the combination of (multiple) daily oral supplements and subcutaneous injections (growth hormone (GH)). Even for patients with normal hypothalamic function, panhypopituitarism requires lifelong adjustments with growth, puberty and stressful situations, making this a challenging situation on its own. Care for patients with HD is challenging and includes a multidisciplinary approach with a (pediatric) endocrinologist, oncologist (if applicable), neurologist, rehabilitation doctor, physiotherapist, dietitian, social work specialist, psychologist and others (14). As HD affects multiple organ systems and functions, it is essential to combine the expertise of various specialists to provide the best care (15). Considering the fact that HD is a rare condition, care should undoubtedly be given in collaboration with an expert center (1).

To provide optimal care and focus future research on the domains that are most relevant for patients, it is important to be informed about how patients perceive current care and which problems they feel should be most urgently addressed. Understanding the unmet needs of patients is especially important with the increasing role of shared decision-making in clinical care over the last years and the inclusion of patient advocacy groups in networks like the European Reference network on Rare Endocrine Conditions (Endo-ERN). This has resulted in recent studies on the unmet clinical and research needs of patients with adrenal crises and patients with rare endocrine conditions (16, 17), but the unmet needs of patients with HD have never been assessed.

This study assesses the most relevant perceived health problems and the unmet social and medical needs of patients with HD following treatment for a suprasellar brain tumor. In addition, patients and caregivers were asked what they would prioritize as research topics to improve outcomes.

Methods

Survey

This research was conducted by the Dutch Pituitary Foundation, in collaboration with the Wilhelmina Children's Hospital and Endo-ERN, with global outreach. An online survey with 25 (sub)questions on the opinions and experiences of patients (and/or parents and caregivers) living with the consequences of acquired HD was developed. The questions were developed by experts in the field (patient representatives and endocrinologists) (Supplementary file 1 and 2, see section on [supplementary materials](#) given at the end of this article). Specialists from Endo-ERN checked the survey on readability. Both open-field questions, single select multiple-choice and multi-select multiple-choice questions were included. The main topics of the questionnaire were socio-demographics, diagnosis and delay in diagnosis, pituitary deficiencies, visual impairment, medication, most important health problems, quality of care, future research topics and the impact of COVID-19. The survey was translated into 14 languages (Bulgarian, Czech, Danish, Dutch, English, Finnish, French, German, Greek, Italian, Norwegian, Portuguese, Spanish and Swedish). The language was checked by native speakers from patient advocacy groups and/or by health-care providers.

The survey was disseminated via a website link through patient advocacy groups, health-care professionals via conferences (SIOPe brain tumor group and ESPE) and via reference centers of Endo-ERN. The survey was constructed using EUSurvey (European Commission). Data were collected between April 1, 2022, and November 1, 2022.

Study population

The inclusion criteria for the survey included patients diagnosed with (1) a suprasellar brain tumor at age < 18 years (self-reported) AND (2) with HD (self-reported). Patients with congenital or unknown causes of HD were excluded. In the situation that the diagnoses of patients were entered at the option 'other diagnosis' with insufficient information to be confident of the fact that these children fulfilled the inclusion criteria for either having had a suprasellar tumor or HD, they were excluded. Examples of patients that we excluded due to uncertainty of the presence of HD are 'panhypopituitarism', 'no functioning pit stalk', 'unknown reason' and 'pituitary failure of unknown

cause'. In these cases, we could not conclude with certainty whether (1) these patients indeed experienced HD (rather than only pituitary dysfunction) or (2) whether the HD was acquired due to a tumor rather than a genetic cause. Patients, caregivers or patients together with caregivers could fill in the survey. For patients under the age of 12, it was recommended to complete the survey by caregivers.

Statistical tests

For descriptive characteristics, proportions were calculated. The chi-square test was used for the comparison of proportions, and the Fisher's exact test was used if more than 20% of the expected values were below five. The *P*-value <0.05 was considered significant.

If applicable for qualitative data, recoding into categories was performed based on the keywords. This was conducted manually by checking all the answers. Machine-based translation using deepl.com was used for the translation of open-field answers to English. Qualitative descriptions of the answers are provided.

For the statistical analyses, SPSS statistical software version 27.0 (IBM) and R version 4.1.2 (R core team, Austria), using packages *ggplot2* and *ggvenn*.

Ethics

Patients consented to the usage of their (anonymous) data for scientific purposes. According to the Dutch IRB, no additional procedures regarding human subject safety were required.

Results

Study population

In total, 374 patients filled in the questionnaire. Twenty-one patients were excluded as they did not have acquired HD but congenital HD or HD of unknown cause. The clinical characteristics of the included 353 patients are shown in [Table 1](#). Patients participated in this study from all continents all over the world, with the highest contribution from Europe (84.4%, [Fig. 1](#)). All included countries are displayed in Supplementary file 2.

The greatest proportion of the patients was aged >18 years (64.6%) while submitting the questionnaire and had been diagnosed with a suprasellar brain tumor more than 10 years ago (53.8%).

Table 1 Descriptive characteristics of the study population ($N = 353$).

Patient characteristics	% (n) from $N = 353$
Sex at birth	
Female	52.4% (185)
Male	46.2% (163)
Would not like to answer/other	1.4% (5)
Current age	
0–5 years	2.0% (7)
6–8 years	3.1% (11)
9–12 years	13.3% (47)
13–15 years	9.9% (35)
16–18 years	7.1% (25)
Above 18 years	64.6% (228)
Diagnosis	
Craniopharyngioma	82.2% (290)
Germ cell tumor	3.4% (12)
Low-grade glioma	3.1% (11)
Pituitary tumor	8.2% (29)
Prolactinoma	2.8% (10)
Hamartoma	0.3% (1)
Time from diagnosis	
Still in diagnostic phase	0.3% (1)
Less than 1 year ago	4.8% (17)
1–2 years ago	8.8% (31)
3–5 years ago	15.3% (54)
6–10 years ago	17.0% (60)
More than 10 years ago	53.8% (190)
Filled in by, % (n/N)	
Patient	61.2% (216)
Caregiver	22.7% (80)
Patient and caregiver together	16.1% (57)

Most of the patients filled in the questionnaire by themselves (61.2%), but for 22.7%, the parent or caregiver submitted the answers. Suprasellar brain tumor diagnosis was craniopharyngioma in 82.2% of the patients, germ cell tumor in 3.4%, LGG in 3.1%, pituitary tumor in 8.2% (including adenoma and Rathke's cleft cyst), prolactinoma in 2.8% and hamartoma in 0.3% of the patients.

Pituitary deficiencies

Deficiency of all anterior pituitary hormones was present in 62.0% (219/353) of the patients. GH deficiency was present in 79.3% of the patients, thyroid-stimulating hormone deficiency in 89.5%, adrenocorticotrophic hormone deficiency in 86.1% and luteinizing hormone/follicle-stimulating hormone deficiency in 77.6%. Posterior pituitary deficiency (arginine vasopressin deficiency) was present in 72.0% (254/353) of the patients; of these, 16.5% (42/254) reported to have had a strict hydration policy, possibly

reflecting the percentage of patients with adipsia. Five patients had not developed any pituitary deficiencies (1.4%).

Diagnostic delay

Patients reported that the time between experiencing the first symptom(s) and date of final brain tumor diagnosis was less than 6 months in 39.9% (141/353). For 37.9% of the patients, diagnosis took more than 1 year from the onset of symptoms (Fig. 2). The time between the first symptom and the date of diagnosis was associated with efforts needed to find the doctor that ultimately made the diagnosis ($P < 0.001$). Patients with a longer time between symptoms and date of diagnosis more often went to another doctor to get the final diagnosis or had to repeatedly ask for a referral.

Most important health problems

Patients were asked to report their three most important health problems at the moment of the survey (Fig. 3A). The three most important reported health problems were obesity (50.7%), fatigue (48.2%) and DI (25.8%). In addition, adrenal insufficiency was reported as the most important health problem in 25.5% of the patients, mood changes in 22.4% and visual problems in 21.8%. For 13.3% of the patients, pubertal delay or gonadal insufficiency/infertility was one of the most important health problems. Six percent (5.9%) of the patients reported short stature as the most important health problem. Other important health problems that were reported by the patients included headache (2.0%), mental health complaints (3.1%), memory loss (1.1%), social problems, such as connecting with others and social anxiety (1.1%), bone problems (0.3%), diabetes mellitus (0.6%), epilepsy (0.6%) and temperature dysregulation (0.8%). In total, six patients (1.7%) indicated that they currently experience no health problems worth mentioning.

Unmet needs and rating of current care for hypothalamic dysfunction

Figure 3B shows an overview of the unmet needs. Most patients receive help with the use of medication (42.8%). Thirty-three percent (32.9%) of the patients reported that no help at all was received for their HD at this moment.

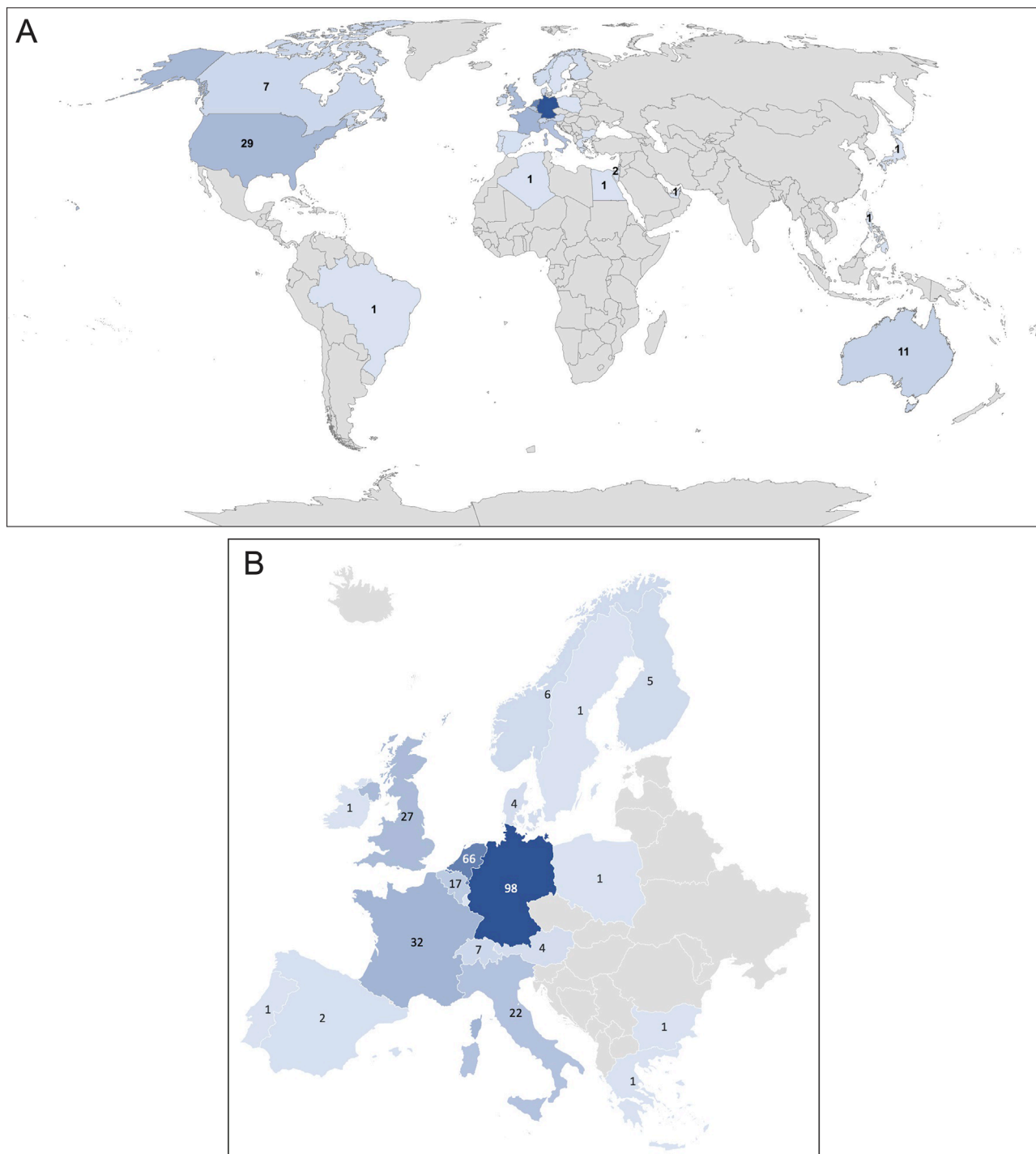


Figure 1
Current country of residence of the study-population. (A) World-wide. (B) In Europe.

Regarding the dietary health domain, 30.9% of the patients had dietary help; however, from these patients, 11.9% (13/109) indicated that they need more help. Of all the patients, 25.2% reported dietary as an unmet need and would like dietary help. For exercise

and sport, 16.4% of the patients reported to receive support, but for 22.1%, it is still lacking.

Psychosocial assistance was currently provided for 19.0% of the patients, but there was an unmet need for 25.5% of the patients.

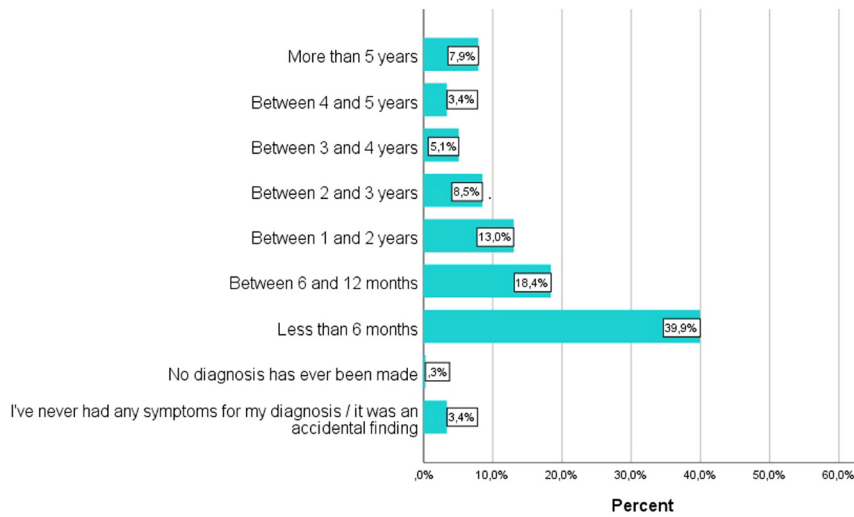


Figure 2

Reported time between symptoms of the suprasellar brain tumor and final diagnosis. Time between the first symptoms to the moment of final diagnosis of the suprasellar brain tumor as reported by patients or their parents/caregivers. The x-axis shows the percentage of patients and the y-axis shows the time between the first symptom(s) and the final diagnosis of brain tumor, as reported by the patient.

In total, 39.4% of the patients indicated that they do not need any additional help in any health domain.

The unmet needs varied according to the country of residence; dietary support was an unmet need for 25.5% in Germany, for 19.7% of patients in the

Netherlands, for 21.9% of patients in France, for 27.6% of patients in the United States (US) and for 44.4% of patients in the United Kingdom (UK) ($P = 0.165$). For psychosocial guidance, there was an unmet need for 26.5% of the patients in Germany, for 25.8% in

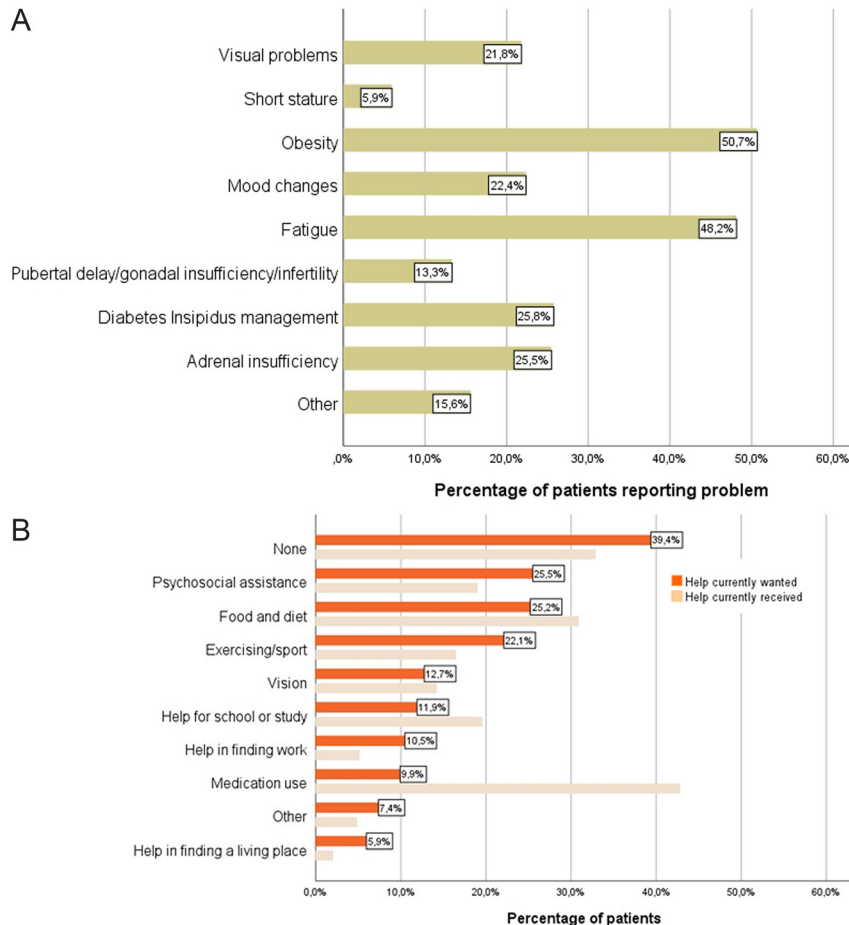


Figure 3

Most important current health problems and current unmet need as reported by the patients. (A) Current health problems. (B) Unmet needs of patients with hypothalamic dysfunction. (A) patients were asked to report their three most important health problems; therefore, the total percentage exceeds 100%.

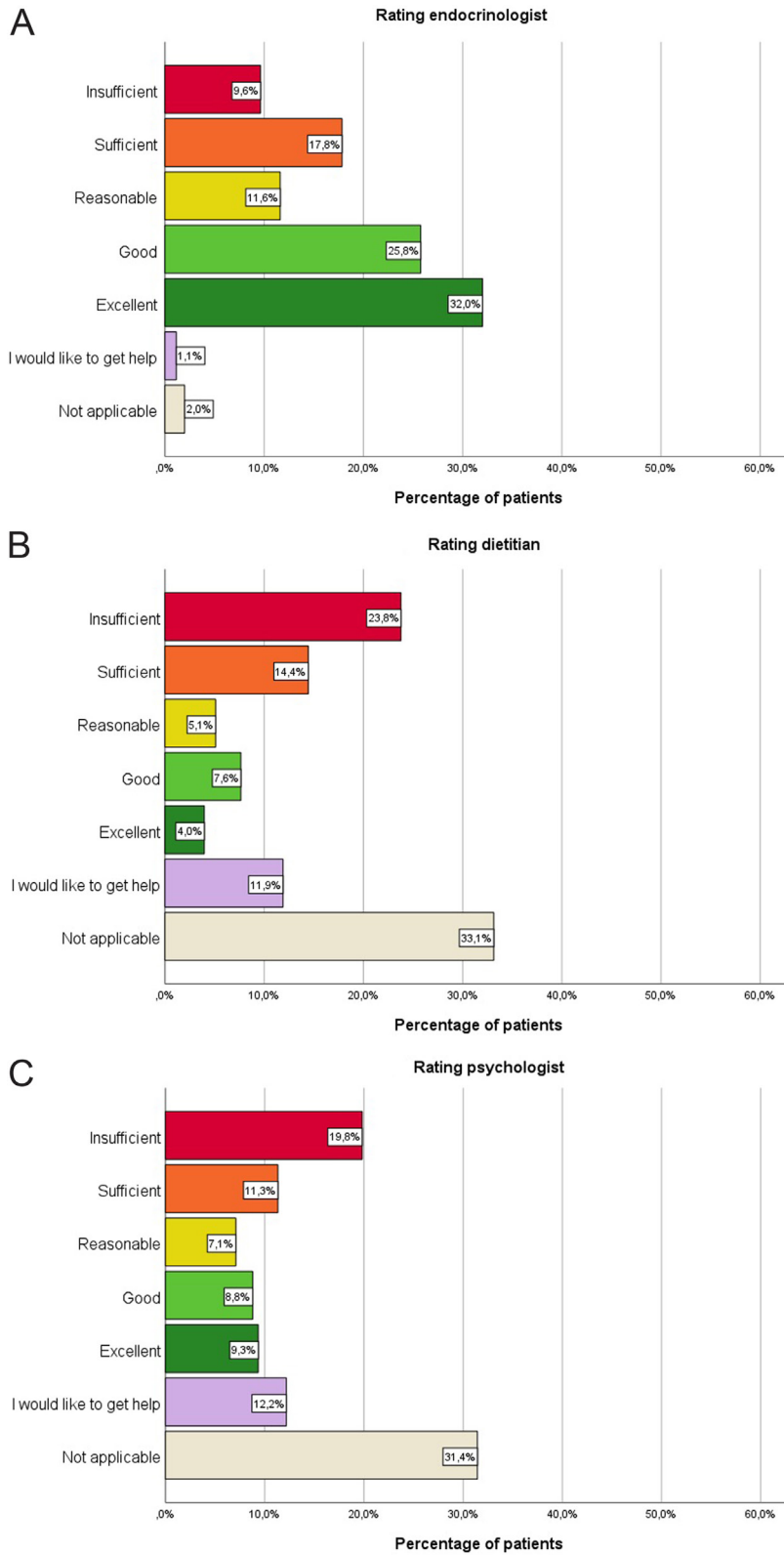


Figure 4
Rating of the guidance that patients receive from various disciplines (A, B, C). Patients were asked how they perceived the guidance or help of various specialists as currently received. (A) Endocrinologist. (B) Dietitian. (C) Psychologist.

the Netherlands, for 6.3% in France, for 34.5% in the US and for 33.3% in the UK ($P=0.077$). For exercise or sport, there was a reported unmet need for 15.3% of the patients in Germany, for 25.8% in the Netherlands, for 21.9% in France, for 37.9% in the US and for 40.7% of patients in the UK ($P=0.022$).

Figure 4 shows the ratings of various specialists according to patients in response to the question: ‘What do you think of the guidance or help you get from the following people: (insufficient, sufficient, reasonable, good, excellent, not applicable, I would like to get help)’.

Most patients qualified their endocrinologist as excellent (32.0%) or good (25.8%), but 9.6% of the patients judged the help of the endocrinologist as insufficient. For dietary support, 4.0% of the patients rated the help as excellent but 23.8% of the patients rated the support of their dietitian as insufficient. Guidance of the psychologist was rated as sufficient to excellent in 36.5%, but insufficient in 19.8% of the patients. More than 30% did not have or need psychological support. Some patients stressed that they would like to receive psychosocial support, and it was felt that it should be a standard addition to the medical treatment, already from an early stage in the disease. According to the patients, psychological support should not only be focused on the patient but also be provided to parents and/or caregivers to help coping with the disease. In addition, patients reported a need for peer support, not only for the patients but also for the parents.

Patients were asked if any additional aspects were currently lacking in the received professional health care regarding the treatment or follow-up of HD. One of the main topics that patients described as current unmet needs was a lack of general information. Several

patients would appreciate a more holistic view of the doctor toward the patient. Because of the fact that patients have to deal with various health professionals, it was suggested to appoint a case manager in place who oversees everything or to create a roadmap of all doctors that were part of the treatment plan of the patient. It was also stated that health care could be improved if more multidisciplinary evaluations were held between experts.

Some patients reported an unmet need for attention to the consequences of the disease on the financial situation of the family. Patients indicated that their parents had to quit their jobs because of their illness and were not able to afford all medication. In addition, not all medication was under assurance or eligible for reimbursement by health insurers. Help was also requested to find a (new) job that fits with having HD and to adapt work to the abilities.

Several patients indicated that they were not aware of the late effects of their brain tumor treatment until they occurred and therefore did not feel prepared for these late effects. According to the patients, some doctors focus too much on survival rather than on quality of life.

Patients’ suggestions for areas of future research

Patients suggested that the focus on future research should be on new treatments for hypothalamic obesity (HO) (26.6%) and alternative ways of hormone substitution (24.9%). The areas for future research selected by ten patients or more are included in Fig. 5. Areas less frequently mentioned for future research as suggested by the patients were improvement of early diagnosis, etiology of the tumor, treatment of the tumor, visual problems, psychosocial aspects, fatigue and more easy detection of adrenal crises.

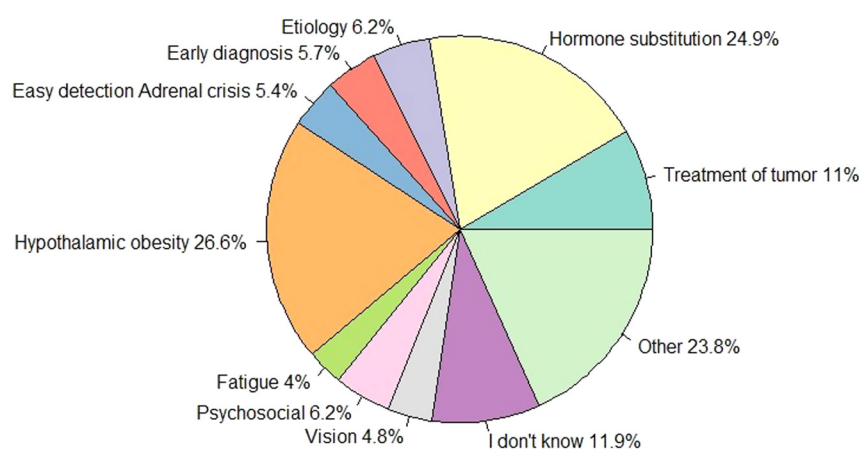


Figure 5

Patient ideas upon the domains for future research. Patients were asked upon their suggestions for future research. Only the topics with more than ten responses are included in the figure. Most patients report that future research should focus on the hypothalamic obesity (26.6%) and alternative/improved ways of hormone substitution therapy (24.9%).

Some more concrete examples given by patients for future research include the introduction of a hydrocortisone pump, or adapting the dose of hydrocortisone to a biomarker, the administration of GH without injection, adjusting the dosage of medication more to individual needs, and possibilities for continuous sodium monitoring for patients with arginine vasopressin deficiency using a smartwatch. To improve visual outcomes, patients suggested research to focus on the possibility to regenerate the optic nerve. Other suggestions for research included various topics, such as the effect of oxytocin on social anxiety and sexual relationships, the effect of various therapies on bones and muscles, acquired brain injury and late effects of medication (on liver and kidneys). In addition, more research was suggested on the relation between the hypothalamic-pituitary axes and the gut microbiome or developing ways to create an artificial pituitary gland or transplant a pituitary gland.

Discussion

HD is a rare devastating condition, which is not always adequately recognized or treated. This unique worldwide survey is the first to assess the patient's (and parent's) perspective of HD after surviving a brain tumor in childhood and to inform upon their unmet needs. The findings of this study can help to create valid recommendations to provide more optimal care for these patients and for prioritization in future research.

For 353 patients with HD, the most important health problems were (hypothalamic) obesity and fatigue. Unmet needs were professional dietary, lifestyle and psychological guidance from diagnosis onward. Between individuals, heterogeneity was found; despite having a tumor in the suprasellar region, not all developed the same problems and not all were impacted in the same way by these problems. The fact that six patients (1.7%) indicated that they currently experience no health problems worth mentioning may be explained by the fact that these patients have a relatively good outcome, or that these patients have the feeling that their symptoms of HD are insurmountable and therefore not worth mentioning. Domains for future research suggested by the patients were finding new treatments for HO and alternative ways of hormone substitution.

Obesity

Despite the fact that more than half of the patients reported HO as the most important problem, which is comparable to the prevalence of HO in literature (18, 19, 20), it was striking to find that there is an unmet need of receiving support or nutritional advice for 25.2% of patients. In addition, 23.8% of patients were unsatisfied with the current care as provided by the dietician. It is unclear from the current survey whether this dissatisfaction results from insufficiently available dietary support or that dietary knowledge on HO is insufficient. It would be interesting to explore how future research could improve hypothalamic dietary expertise leading to subsequent specific hypothalamic dietary advice.

Patients indicated that they need more support with exercise and sports (reported by 22.1%). Comparable to 'general' obesity, combined lifestyle intervention remains the cornerstone of treatment for HO (21, 22). Physical exercise is of special importance due to the fact that exercise will increase muscle mass, and improved muscle mass will improve resting energy expenditure (23, 24). Early referral to a physical therapist or lifestyle program is recommended to give proper advice on exercise and energy. Also, patients suggested HO as one of the main research topics, similar to a previous questionnaire for caregivers of children with craniopharyngioma (25).

Fatigue

Next to obesity, fatigue was considered one of the most important health problems. Fatigue is not an explicit symptom and, in patients with HD, can be a reflection of many different underlying causes such as sleep problems, hypothermia, fluctuating sodium concentrations, inadequate hormone substitution or a general feeling of a lack of energy due to worries or psychosocial problems. A retrospective review on craniopharyngioma patients reported fatigue to be present in 67.9% of the patients (26). Greater hypothalamic involvement was associated with fragmented sleep in a study with actigraphy use (27). The fact that in our survey the percentage of patients reporting fatigue (48.2%) was different from the patients suggesting fatigue as a research topic (3.7%) was striking and was different in a previously published online questionnaire for caregivers of children with craniopharyngioma where fatigue was reported as an important research topic in almost 50% (25). This may

be explained by a belief of patients that fatigue is an insurmountable result of having (treatment of) a brain tumor. Complaints on fatigue in patients with HD should be further explored by dividing this symptom into various domains to explore underlying causes and possible ways for improvement.

Patients reported psychological help as insufficient, with 25.5% indicating to want help from a psychologist. This is an important finding as it was previously shown that psychological status influences long-term health in cancer survivors (28, 29). As the unmet needs varied for different countries, it is useful to explore this further.

Early diagnosis

Because tumors with hypothalamic involvement are often closely related to the visual pathways, they can cause irreparable damage (30, 31). In addition, the greater the involvement of the hypothalamic region at the time of diagnosis, the greater the hypothalamic consequences will be (32, 33). For this reason, the early diagnosis is of utmost importance. In a substantial proportion of patients (37.9%), there was a gap of more than 1 year between the first presenting symptom and the final diagnosis of the suprasellar brain tumor. Being aware of the manifestations of HD may support early diagnosis (34).

Suggestions for future research

Propositions for research especially included alternative ways to administer medication, if possible via an adaptive pump system with measurement of hydrocortisone or sodium levels at home (35, 36). Pharmaceutical companies are increasingly focusing on other ways to deliver medication into the bloodstream for children (37, 38). Still, only 9.9% of the patients indicated that additional help is needed in the domain of pituitary insufficiency, possibly reflecting that current care for these patients is adequate or they accept their destiny.

Strengths and limitations

Our survey has several limitations. We aimed to include as many as possible patients with a suprasellar brain tumor and subsequent HD and were able to reach a large number of patients. Unfortunately, the distribution of patients that entered the questionnaire was not congruent with the prevalence of suprasellar brain tumors. Despite our efforts to include a more

heterogeneous population, most of the participants were diagnosed with craniopharyngioma (82.2%). Despite the fact that HD is also prevalent in LGG, this is still a new and relatively unrecognized entity in these patients. Therefore, patients with LGG are less frequently affiliated with a patient advocacy group representing endocrine problems. All answers to the questionnaire were patient-reported outcomes. Although we manually checked all open-field answers on compliance with the inclusion criteria, the histological diagnosis of the tumor (including location) could not be checked for correctness. Also the prevalence of pituitary deficiencies in this study may be an under- or overestimation as self-reporting of endocrine deficiencies by patients may not always be reliable. By translating the questionnaire into 14 languages and by the review for readability by native speakers, the barriers to participate internationally were tried to overcome. Most of the responses were from countries in Europe, due to the absence of patient organization groups in a lot of other continents or elaborate ethical procedures.

In 16.1%, the parents or caregivers filled in the questionnaire instead of the patients themselves, of which in some cases even for children older than 12 years, which may be related to the cognitive capacity of the patient. To have the survey filled in by caregivers might have influenced the results as caregivers may have a different view of the unmet needs. Finally, a selection bias may be present as it can be hypothesized that patients with more severe HD are more likely to actively participate in disease-related surveys. On the other hand, patients without stable disease may not have been able to participate due to other disease-related priorities.

Conclusion

In conclusion, this survey reflects a first inventory of the patient's unmet needs, when confronted with acquired HD due to a suprasellar brain tumor or its treatment during childhood. According to the patients, the focus of treatment should not only lay on survival but also on the quality of life after survival. Ideally, the care for patients with HD should be provided by a multidisciplinary expert team with a holistic view of the patient. In the current setting of personalized medicine and shared decision-making it is essential to adapt clinical care and research to patient needs.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-23-0147>.

Declaration of interest

Authors have no conflict of interest to declare

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Author contribution statement

Conception and design: IMAA van Roessel, JP de Graaf, HM van Santen, NR Biermasz, E Charmandari. Collection and assembly of data: IMAA van Roessel and JP de Graaf. Data analysis and interpretation: all authors. Manuscript writing: all authors. Final approval: all authors. Accountable for all aspects of the work: all authors.

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