Best Practice & Research Clinical Endocrinology & Metabolism 33 (2019) 101309

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

The burden of disease for pituitary patients

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ARTICLE INFO

Article history:
Available online 2 August 2019

Keywords:
acromegaly
Cushing
prolactinoma
non-functioning pituitary adenoma
endoscopic surgery
quality of life

Pituitary diseases are rare conditions with severe chronic multiorgan and multisystemic morbidity requiring complex multidisciplinary treatment and usually life-long drug treatment. Most cases are caused by functioning or non-functioning pituitary adenoma. From the patient's perspective, the burden of disease is caused by the tumour itself and associated compression symptoms, interventions, hormone excess and deficiencies, systemic manifestations of these endocrine abnormalities and general psychosocial issues that can manifest in patients with a chronic condition. In this review, patient burden is classified according to classic endocrine syndromes, with burden at diagnosis and after long-term remission, and also within the framework of value-based health care and the conceptual model of wellbeing. The recently developed patient-reported outcome measurement tool that helps to evaluate burden of patients is also discussed.

Introduction

Pituitary diseases are rare conditions with severe chronic multiorgan and multisystemic morbidity requiring complex multidisciplinary treatment and usually life-long drug treatment. Most cases are caused by functioning or non-functioning pituitary adenoma. The burden of patients with pituitary conditions is considered severe and chronic, as these patients usually need life-long care and treatment. Daily life remains affected despite long-term remission.

The causes of disease burden for patients are numerous. First, the tumour may result in compression symptoms, and interventions are likely to be associated with complications and side-effects. Hormone excess and deficiencies result in specific symptoms and systemic manifestations.

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https://doi.org/10.1016/j.beem.2019.101309
1521-690X/

All general psychosocial issues that manifest in patients with chronic conditions also apply to patients with chronic pituitary disease.

In this review, patient burden is classified according to specific endocrine syndromes, burden at diagnosis and after long-term remission. Patient burden is first described within the context of classical endocrine hormone excess and deficiency syndromes. Recently published late outcome studies that evaluate burden are then discussed.

Next, we elaborate burden according to the framework of value-based health care, focusing on a comprehensive set of outcome measures [1]. The conceptual model of wellbeing by Wilson and Cleary is used to classify the various aspects of burden from a biopsychosocial perspective [2,3].

In pituitary disease, core clinical outcome sets and patient-reported outcome sets have not been well developed. Currently available patient-reported outcome measurements that may help to evaluate clinical burden of patients in patient care and research, and future research, are discussed [4–7].

Patient burden: textbook description of endocrine syndromes

Pituitary diseases are rare conditions that can be classified into hormone overproduction syndromes, hormone deficiency syndromes and mass effects syndromes, causing compression of structures in the vicinity of the pituitary. A subset of patients presents with congenital forms of hypopituitarism in childhood with or without dysmorphic features. In this review, we focus on adults and conditions around pituitary adenomas. Clinical manifestations and patient burden of individual pituitary syndromes are detailed below (Table 1).

Acromegaly

Acromegaly is a rare disease caused by overproduction of growth hormone and, consequently, from insulin-like growth factor 1 (IGF-I) from a pituitary adenoma producing growth hormone. Progressive changes result in facial appearance and typically growth of *acra* (hands and feet and facial features). Internally, organs also grow, resulting in many comorbid conditions, such as cardiomyopathy, osteoarthritis caused by cartilage hypertrophy, colonic polyps, obstructive sleep apnoea syndrome and altered bone architecture. Growth hormone treatment causes sodium and water retention, resulting in hypertension and carpal tunnel syndrome. Other symptoms include headache, sweating, fatigue and mental effect of the disease [8–10].

The imbalance of hormones usually affects other hormone systems, resulting in hypogonadism, diabetes mellitus and glucose intolerance, and renal stone formation. The patient usually has a diagnostic delay of several years and may present with severe complaints, although some patients have few symptoms at start. Treatment is indicated to limit late effects of acromegaly on co-morbidity and mortality, to improve current and future symptoms and health-related quality of life (HR-QOL) and to

Table 1
Patient burden and individual treatment goals.

Current and future burden of pituitary disease. Individual treatment goals for intervention
Current burden:
Decompression of the optic system (visual symptoms)
Relief of hormone excess (symptoms and co-morbidity)
Relief of local pressure (headache)
Improve pituitary function (if hypopituitarism, suppression of gonadal axis)
Improve symptoms (if present and due to pituitary condition)
Improve HR-QoL (if impaired)
Tissue diagnosis to guide therapy
Resolve CSF leak
Chance to stop or lower dose of drug (improve side effects)
Future burden:
Prevent consequences of hormone overproduction (Increased mortality, co-morbidity, symptoms)
Prevent future visual compression and optic nerve damage
Prevent impaired HR-QOL

establish tumour control [11–13]. Normalization of growth hormone overproduction usually improves symptoms and comorbid conditions, although late effects may persist, and co-morbidity may not be reversible. Some patients do not achieve full remission but rather achieve some degree of biochemical control of the disease. Untreated acromegaly is associated with 2–3-fold increased mortality and treated acromegaly improves this risk to a near normalized risk of 1–1.3-fold increased mortality [14].

Cushing's disease

Cushing's disease is a rare disease usually caused by a pituitary adenoma which produces adrenocorticotropic hormone (ACTH). Other forms are ACTH-independent adrenal tumours or ACTH-dependent ectopic lesions [15]. The burden of disease at diagnosis is caused by high levels of cortisol, and symptoms usually include fatigue, proximal muscle weakness, sleeping problems, psychological problems, changes in appearance (moon face, buffalo hump, central obesity) and skin atrophy (striae, easy bruising). Comorbid conditions include hypertension, diabetes, infections, thromboembolic processes and hypogonadism [16]. Diagnostic delays usually occur, with vague, progressive symptoms developing over months or years. After diagnosis, some patients will undergo a complicated work-up because initially the differentiation between hypercortisolism and eucortisolism is not straightforward, and the source of Cushing's disease can be hidden (e.g. a tiny microadenoma in the pituitary, multiple locations or an ectopic source). Some patients may require testing and retesting, and adds a further burden in the form of insecurity about what is happening. In cases of total surgical resection, cortisol levels drop to low levels, which is a good predictor of success, but coincides with severe withdrawal syndrome, including musculoskeletal pains and mental vulnerability. Although supraphysiologic steroid replacement may help, quality of life is affected. The hypothalamic pituitary adrenal axis usually restores after a few months to years. Risk of systemic complications is increased in the first year and normalizes afterwards [17,18]. Mortality, however, is high for this group [18]. Risk of recurrence of Cushing's disease is expected [19].

Prolactinoma

Prolactinoma is one of the more common pituitary adenomas, although it is still a rare disease [20]. Prolactinomas have several clinical manifestations. Typically, premenopausal women present with smaller micro or macroadenoma, with amenorrhoea, galactorrhoea and infertility. A specific burden of the disease is infertility [21]. Usually, these tumours respond to drug treatment and may be cured by medical treatment. A small subset of patients undergoing drug treatment experience severe side-effects [22,23], whereas others face mild side-effects. Larger prolactinomas and giant prolactinomas usually occur in men, with good responsiveness to drug treatment albeit at a higher dose in some; however, visual symptoms and hypogonadism may occur [24].

Non-functioning adenoma

Non-functioning adenoma is the most prevalent pituitary adenoma. Visual symptoms and hypopituitarism usually occur [25,26]. Visual field defects improve after treatment, although in some cases persisting abnormalities remain. Tumour remnants require surveillance and, if not irradiated, are at significant risk of regrowth. Tumours may present as giant adenoma with increased surgical risks for removal. Increasingly, patients may present with incidentaloma, small tumours identified by a scan for another reason [27]. Although asymptomatic, patients may experience psychological burden [2].

Acquired hypopituitarism in adults

Acquired hypopituitarism in adults may occur as a result of the tumour, tumour treatment, from a congenital cause, inflammation or irradiation. Presenting symptoms are usually non-specific, and diagnosis is therefore difficult. The growth hormone IGF-I axis and the hypothalamic pituitary adrenal axis may require dynamic testing.

Replacement of all axes is possible, and clinical symptoms usually improve; however, persisting complaints are well known. Panhypopituitarism, which also includes diabetes insipidus, is the most severe form, and this condition is associated with more burden, including risk for Addisonian crises [28].

Patient burden at diagnosis: treatment goals

Patients may have small or large tumours and functioning or non-functioning tumours; therefore, they may present with symptoms or no symptoms at all, and disease burden at presentation will vary widely. Therefore, it is important to define individual treatment goals and to discuss with patients why an intervention is indicated and what can be expected. The goal of an intervention may be current burden or rather to prevent future burden. This will depend on the individual's situation.

Aftermath of endocrine syndromes: chronic burden of pituitary disease

Over the past 10–15 years, awareness of pituitary diseases has increased. The overproduction syndromes acromegaly, Cushing's disease, craniopharyngioma and chronic hypopituitarism, in particular, have chronic, long-lasting consequences for the patient. Quality of life, as measured by physical function and mental subscales, is severely affected in the active stage, and improves but does not normalize after successful medical treatment. Several studies have addressed long-term outcome with respect to bodily functions. The full spectrum of long-term complications is abundant, and addressed elsewhere [8,16] (Table 1).

Patients with acromegaly suffer from joint pain and stiffness [29–31]. This is a result of secondary osteoarthritis, a degenerative joint disease that persists after remission. Typically, all joints are affected at a younger age, are more severe than in the general population and include cartilage hypertrophy and severe osteophytosis. It is a chronic irreversible complication; however, good control of acromegaly tends to stabilize the condition, and in some cases physiotherapy is beneficial. Individual joints may benefit from replacement surgery in late-stage disease. Also, vertebral fractures tend to occur more often, especially in patients with hypogonadism. Hypertension is more frequently present than in the general population. Colon problems, a dolichocolon and polyps are induced by growth hormones and may cause symptoms. Jaw problems and sleep apnoea syndrome may persist [8]. Headache and fatigue may be refractory to treatment [7]. Surgery alone is insufficient for most patients with invasive tumours. Multimodality treatment of acromegaly is usually well tolerated, although some patients experience chronic burden of injections, with symptoms that wear off at the end of the somatostatin receptor ligand injection intervals [32]. Combination therapy of pegvisomant and somatostatin analogues may improve HR-QoL irrespective of improved IGF-I control [33]. Radiotherapy results in hypopituitarism and delayed remission, and is associated with impaired HR-QoL [34].

Direct comparison of various treatments has not been undertaken, precluding a scientific answer to which treatment is best to achieve optimal functional outcome. Usually, activity of disease at diagnosis and growth hormone activity during follow-up, e.g. well controlled or uncontrolled, is associated with progression of comorbidities [35]. Long term, patients who have undergone treatment suffer from impaired HR-QoL on all scales. Neuropsychiatric assessment of patients in long-term remission reveal subtle abnormalities [36].

Patients with Cushing's disease have impaired HR-QoL [37–39]. Mortality scores remain elevated after treatment as well as prevalence of several co-morbidities (fractures, hypertension, cardiovascular events) [17,18,40]. Infections and thromboembolic complications are no more prevalent in late follow-up. HR-QoL is severely affected in many patients, and neurocognitive complaints are an important issue [41–43]. Measurement of memory and cognition reveal abnormalities within the spectrum of normal, but, as a group, patients with remitted Cushing's disease are impaired. Structural and functional magnetic resonance imaging scanning is able to detect abnormalities in this patient group [43,44].

The burden of disease in patients with prolactinoma is not well characterized in the long-term. The idea that an episode of drugs results in remission may not be true for most patients [45]. In a subset of patients, dopamine agonists cause side-effects, but many patients tolerate the drug well. HR-QoL seems to be affected in small-sized studies [22,23,38].

Burden in non-functioning tumours is mainly a consequence of pituitary failure and consequent adrenal failure and growth hormone deficiency. Therefore, optimal hormone titration is key, and data from this group can be derived from growth hormone deficiency studies, adrenal insufficiency studies as well as studies on non-functioning pituitary macroadenomas [2,26,46–49]. Mortality is slightly increased and HR-QoL is reduced. Some data show that patients with previous suprasellar tumours experience more sleeping disturbances than the general population, which may be caused by subtle hypothalamic dysregulation [50,51].

Patient burden and health outcomes of an intervention: care path as categorized in the three-tier model by Porter

In pituitary care, treatment options are not compared head to head in controlled studies; therefore, comprehensive clinical outcomes, including patient perceptions and expectations, are not well known for interventions separately. This is an extreme challenge, as clinically relevant outcomes in pituitary disorders have not been well defined, and no consensus has been reached on a core clinical outcome set. Indications for treatment vary, and multimodality treatment is warranted in most patients. This complicates the evaluation of a single intervention. This is a plea for treatment in centres of expertise [12,52].

A potential framework for assessing outcomes is the Value Based Health Care (VHBC) framework, originally developed by Michael Porter and Elizabeth Teisberg. This aims to increase value for the patient by improving patient-relevant outcomes and decreasing costs [1].

In this framework, outcomes are categorized into a 'three tier hierarchy', reflecting perceived relevance for patients [1]: the health status achieved or retained [2]; the process of recovery; and [3] the sustainability of health. Outcomes can be measured around an intervention or a better care path (e.g. the surgical care path) but these are the composite results of the medical condition plus the full cycle of care. Therefore, in this framework, surgical intervention as well as in- and outpatient hospital care and rehabilitation are assessed. Health outcomes are traditionally described through clinician-reported disease parameters, such as degree of tumour resection, restoration of hormone hypersecretion (remission) and recovery of visual field deficits or visual acuity, although HR-QoL is increasingly evaluated [7,53,54]. The VBHC approach also advocates patient-reported outcome measures to assess the extent of the disease, the effect of treatment on a patient's functioning and HR-QoL, and ultimate functional outcome. Below, the burden for pituitary disease and patient relevant outcomes as classified in the VBHC framework are discussed (Table 2).

Table 2
Areas of burden and health outcomes for pituitary disease classified in the VBHC framework.

Tier 1 (Health status achieved or retained)
Survival
Remission of hormone overproduction
Recovery of visual field defects
Recovery of impaired pituitary function
Degree of resection
Recovery of symptoms, impaired HR-QoL, health status
Tier 2 (Process of recovery)
Course of recovery (symptoms, HR-QoL)
Hospital stay
Complications
Time to return to work
Tier 3 (Sustainability of health)
Recurrence rate
Additional interventions needed
Permanent hypopituitarism and replacement
Comorbidities due to disease and intervention

Tier 1: health status achieved or retained

Potential relevant Tier 1 core outcomes could be survival, remission of hormone overproduction in functioning tumours, visual recovery in patients with visual field defects, recovery of impaired pituitary function in those with preoperative hypopituitarism, degree of resection based on neurosurgical and radiological evaluation and recovery in patient-reported outcome (e.g. quality of life or health status).

Survival

Pituitary surgery has negligible perioperative mortality. Long-term mortality studies of pituitary patients are available; however, larger studies include patients in their seventies or eighties who have undergone treatment with older drugs as present-day treatments were not available at that time (.g. radiotherapy was used more frequently). Therefore, caution is warranted when extrapolating to current practice. In treated acromegaly, mortality increases 1–1.3-fold. Predictors of disease activity are hydrocortisone dependency, radiotherapy, and diabetes and hypertension [14,55–57]. In treated Cushing's disease, mortality increases 1.5–2.5-fold, and the number of interventions is acknowledged as an important factor [17,18,40]. In non-functioning adenoma, there is no clear increase in mortality compared with hypopituitarism and growth hormone deficiency [26].

Remission of hormone overproduction

Hormone overproduction is related to many symptoms and comorbidities, and is therefore a biomarker of burden of patients. Symptoms and biochemistry are not 1:1 related, so, for example, burden from a (transient) severe steroid withdrawal syndrome may coincide with successful biochemical remission of Cushing's disease. Nevertheless, experts agree that we should strive for biochemical remission. Optimal chances for remission can be achieved by surgery in a specialized unit, and use of multimodality treatments, including drug treatment, according to current guidelines [19,52,58]. Individual factors are important considerations as the chances for remission vary from patient to patient (e.g. tumour size and extension). Available data are derived from retrospective surgical and radiotherapeutic case series and medical treatment trials. Meta-analysis of these data reflects these remission rates and therefore may predict post-treatment burden for patients.

Visual recovery

Visual recovery after decompression surgery is usually effective. In general, patients with visual field defects and even visual acuity deterioration will experience improvement of function, and this will improve burden-related preoperative impairment [59]. A small subset of patients, however, will have persisting abnormalities with variable effects on health status. Prevention of visual symptoms in future is an indication for surgery in a subset of patients; in those, the result of the intervention will not be easily measurable (e.g. no effect on visual function, albeit with a chance of deterioration as other health outcomes). Research on patient perception of such a preventive intervention is currently lacking, and therefore optimal timing of these cases is a matter of debate. In clinical practice, some patients tend to prefer a wait and see policy, whereas others prefer an intervention rather than waiting, so an individualized approach taking into account age and tendency of growth seems reasonable.

Improvement of hormone deficits

The exact figures may vary between 0 and 20%, with unreliable predictive factors. The burden of patients will likely improve with less hypopituitarism and less replacement needed. Therefore, it is an important outcome measure to include in the surgical result [59].

The degree of resection

The degree of resection is an outcome for describing surgical success and may be related to patient burden, in the context of need for surveillance, re-intervention, chance of recurrence, persisting complaints and, of course, the perception of dealing with a remnant tumour. The degree of resection is dependent on the preoperative tumour size and extension, and the chances of tumour resection versus preservation of pituitary function should be weighed carefully [53].

Quality of life and health status achieved

The recovery in quality of life and health status after an intervention has been studied incompletely. Few prospective and longitudinal quality-of-life data in surgical studies that generally report an improvement by intervention have been published. Long-term cross-sectional data reflect a suboptimal quality of life. Health status has not been assessed extensively; however, it is important to note that EQ5D (generic daily life functioning) is usually quite normal, although fatigue, mental scales and disease-specific questionnaires (e.g. ACROQOL) report important limitations after treatment [38,53].

Tier 2: process of recovery

The course of recovery of disease burden after surgery is highly individual. Visual functions recover immediately, although maximal improvement can take months. The recovery of hormone overproduction is likely immediate, although in Cushing's disease anecdotal cases have shown delayed remission. The course of symptoms (self-perceived recovery), HRQoL, including utility-scales and time to return to work, are not well studied. Reference values are not available. HRQoL usually improves, depending on disease severity preoperatively; however, some patients will experience a decline in HRQoL, mainly patients with Cushing's syndrome and those with new pituitary failure, although some are unexplained [53,60].

Ineffective interventions, the length of the care process and prolonged hospital stay can be a burden in complicated cases. The standard duration of admission is highly variable per institution, ranging from 2 to 3 days to up to a week or more, based on expert opinion and local situation. Neurosurgical complications, such as postoperative cerebrospinal fluid leak, meningitis and epistaxis, are reasons for prolonged stay, and usually the consequences are not permanent [54].

Nasal morbidity needs to be considered, but usually this will resolve after 6 weeks.

Postoperative complications may occur, in most cases transient diabetes insipidus and (readmissions for) hyponatremia (5–15%). The main long-term complication is hypopituitarism and permanent diabetes insipidus, which occurs in less than 5% of cases, albeit depending on tumour size and relation to the stalk.

Tier 3: sustainability of health

Sustainability of health in the long-term may comprise first the ultimate number of patients with permanent deficiencies, the proportion of cases requiring re-interventions for persisting and recurrent diseases, and replacement therapies. It also comprises the proportion of patients with co-morbidity (related to intervention and disease) which is, of course, highly dependent on the underlying condition. Consequently, this would be a large outcome set, including many comorbidities [8,16,19,45].

This framework could be used as a way of reporting outcomes of a targeted intervention or a care path for patients with various pituitary tumours by using a comprehensive set of clinical and patient-reported outcomes. Burden seems highly variable between individuals and tumour types, and more data are needed to draw conclusions and establish factors of influence. To date, no comprehensive datasets assess all patient-relevant data. Many studies, however, report remission rates, recurrence rate and complications. With HR-QoL, the limited number of studies that do report results show an increase in HR-QoL after surgical intervention compared with preoperative outcomes, usually with generic rather than disease-specific questionnaires [48].

Finally, to further elaborate on the value for the patient alongside the framework of VBHC, it is also necessary to evaluate the cost of treatment, as value can be increased by improving outcomes, but also by lowering costs [61].

A biopsychosocial model of patient burden and wellbeing

As a uniform definition of HR-QoL is lacking, evaluation and interpretation of HR- QoL is challenging. Experts, however, agree that HR-QoL should cover physical (bio), psychological and social aspects of wellbeing. A frequently used definition of HR-QoL is ‘the functional effect of an illness and its consequent treatment upon a patient, as perceived by the patient’. Optimal biomedical multimodality treatment, e.g. surgery, drug treatment and radiotherapy, aimed at normalizing biochemistry, which traditionally has been the focus of healthcare professionals, does not result in normalized HR-QoL [48]. Therefore, it is hypothesized that potential further improvement of HR-QoL could be established by addressing other elements, such as patient characteristics and the (healthcare) environment, using psychosocial care modalities (e.g. self-management training, psychological support). This has been established for other chronic diseases.

The conceptual model proposed by Wilson and Cleary (1995) is frequently used to conceptualize HR-QoL [3]. This model is supported by empirical evidence and has been widely applied to different conditions. The biopsychosocial model integrates the clinical paradigm (i.e. the biomedical paradigm with its biological, physiological, and clinical outcomes) and the quality of life model (i.e. social science paradigm with its functional status and overall wellbeing). Health is considered as a continuum of increasing biological, psychological and social complexity: one side represents pure biological measures and the other side represents general health perceptions (Fig. 1). It connects the cell to the individual and the individual to the social context. In a recent review, this model was elaborated for patients with non-functioning pituitary macroadenomas and below a modification is made for all pituitary disease with main causal relationships and mediating factors but of course many underlying complex interactions [2]. The association between symptom status and biophysiological variables is rather complex. Although biophysiological variables can be profoundly abnormal, a patient may not perceive any symptoms or, on the contrary, a patient may be disabled while biological parameters are considered within the reference range.

Biological and physiological variables

In pituitary diseases, many biological and physiological variables are disturbed. A pituitary mass develops, with the potential for compressive mass effects (visual system, pituitary dysfunction, sometimes hypothalamic dysfunction) or the treatment may affect the endocrine system. This situation is not easily normalized.

Endocrinologists are well aware of the many technical challenges in identifying optimal homeostasis in an individual patient with an endocrine disorder, as subtle hypopituitarism and abnormal circadian physiology will affect wellbeing; however, these are difficult to diagnose with current endocrine tests, owing to age and gender-dependent reference ranges, hormone sensitivity and

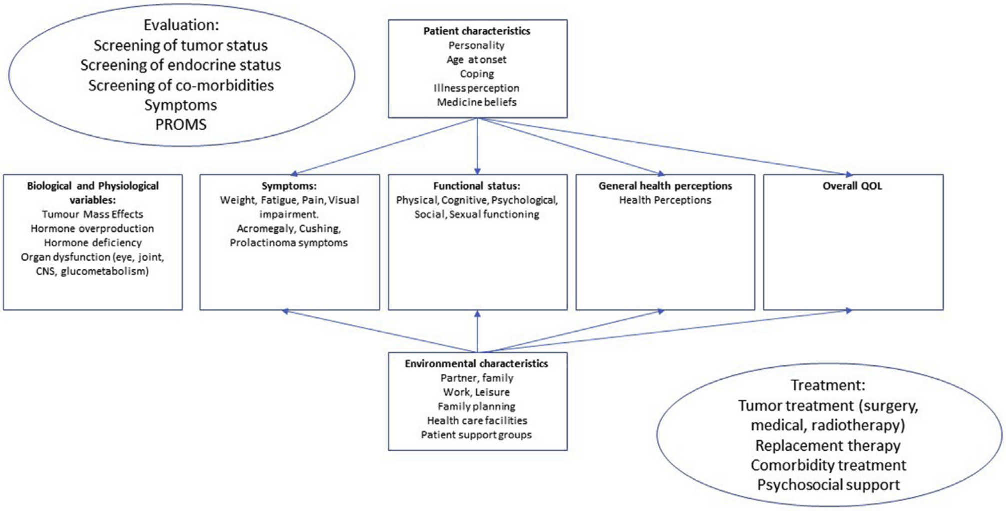

Fig. 1. Burden of disease in pituitary patients: the conceptual model of HR-QOL proposed by Wilson and Cleary [3] and diagnostic and therapeutic interventions.

individual set points. Better individualized titration of hormone deficits is clearly needed to improve HR-QoL. In hormone overproduction syndromes, the multimodality treatment needed should also be individualized to achieve optimal endocrine control, and ideally restoration of physiology to optimize HR-QoL [33]. Probably these biological factors are strong determinants of HR-QoL in active hormone overproduction syndromes.

Symptom status

Alterations in biophysiological variables may be perceived by their symptoms. According to Wilson and Cleary [7], symptom status is defined as a patient's perception of an abnormal physical, emotional or cognitive state. Perceived symptoms of a tumour can be pain, pituitary failure, visual impairment, fatigue or decreased libido. These usually improve after decompressive surgery; however, extensive longitudinal research on the course of symptoms is limited to pharmaceutical trials [7]. Most presenting symptoms are well treated with surgical or medical intervention. Symptoms, however, persist. In pituitary patients with chronic disease, the following symptoms have been reported: physical pain, altered sleeping, changes in physical appearance (i.e. weight changes and facial features), neurocognitive issues (i.e. concentration, memory and executive functioning), sexual dysfunction, depressive symptoms, mood swings, worries, increased sensitivity to stress, fear of tumour recurrence, decreased self-esteem and a lack of empathy from the social environment [46]. In overproduction syndromes, classical symptoms are present (see above the description of syndromes). For acromegaly, the PASQ symptom list provides clinical experience. These acromegaly-specific symptoms improve with treatment but do not completely resolve with optimal treatment, so a component of symptoms is probably irreversible despite optimal medical treatment [7]. In acromegaly, joint symptoms are a main symptom for patients, which seem to be associated with quality of life [29]. In analogy, fatigue and sleeping problems occur in many patients, and this symptom is associated with quality of life so these comorbidities are important to address in an attempt to improve HR-QoL [50]. In the short term, an intervention will increase symptomatology. Perceived symptoms of surgical procedure can be headache and nasal symptoms (impaired smell, taste and nasal obstruction) [53]. Other endocrine syndromes have disease-specific symptoms (e.g. prolactinoma) with clear effect on gonadal status, which usually quickly resolve upon treatment.

Functional status

Functional status means the ability to perform specified tasks. The perception of functional status is largely determined by the symptom status. The perceived symptoms result in impairments in several functional domains. Patients report problems in several domains (e.g. physical, cognitive, sexual, psychological and social functioning) [6,48]. For instance, work-related problems include diminished ability to be productive and to concentrate, with job loss in a significant number of patients [60]. Cognitive complaints have been confirmed by subtle abnormal neuropsychological function tests, in particular in patients with prior Cushing's disease [42,44]. Physical symptoms and functional impairments caused by arthropathy are predominantly present in acromegaly [30].

Characteristics of the individual

Individual patient characteristics in the biopsychosocial model cover factors such as personality, motivation, values, beliefs and preferences. Patients' preferences or values refer to the value a patient attaches to a consequence of the health condition. For instance, a patient can experience a symptom as a burden, whereas, another patient does not bother at all about this symptom. How a patient perceives his or her illness and the applied treatment is known as ‘illness perceptions’ and ‘beliefs about medication’ [41,62–67]. Patient perceptions were associated with HR-QoL in a group of chronic pituitary patients, and this study revealed large differences between patients [41]. In particular, the belief in medication (e.g. ideas on potential side-effects) is a clinically relevant topic in pituitary patient care, in patients replaced with hydrocortisone and when there is a choice between interventions with drugs or surgery.

The perception of illness and beliefs about medicines influence a patient's coping behaviour. Pituitary patients report fewer efficient coping strategies, such as withdrawal and overdoing activities. Patients were reported as having fewer active coping strategies, seeking less social support and using more avoidance. Patients with pituitary conditions, especially those with functioning tumours, report changed personality.

Characteristics of the environment

Psychological, social and economic support play an important role in general health perception and determine overall wellbeing. In a focus group study, patients reported unmet needs regarding care and guidance (e.g. patient information about adverse effects of medication, consequences on physical and cognitive complaints and issues regarding sexual functioning and work related issues) [46,68]. The patients missed recognition of certain complaints. For example, patients reported dissatisfaction with other aspects of medical care, i.e. stress-management training, lifestyle recommendations, physiotherapy, rehabilitation and psychologists. The delay in diagnosis is a topic that matters to patients in several ways [69].

Support of partner and support of social network are also recognized areas for improvement. Many patients face social isolation. The partner usually is the most important person in a patient's social network. From focus-group conversations with partners, we have learned that partners worry about the complaints of the pituitary disease, in particular Addisonian crises, have negative beliefs about medication, perceived coping challenges, relationship and work-related issues, and have unmet needs regarding care that they should be taken into account in chronic care [68].

General health perceptions and HR-QoL

All domains described in the preceding paragraphs contribute to HR-QoL as perceived by the patient.

The Wilson—Cleary model accentuates the awareness that persistent impairments in HR-QoL might be explained by issues at each stage of this bio-psycho-social model. It highlights the complexity of HR-QoL, explains individual variation and provides targets for intervention. Improvement in overall HR-QoL requires optimal biomedical treatment with a better symptom status and also attention for the other elements. Interventions that pay attention to cognitive functioning, psychological wellbeing, coping behaviour, self-efficacy, social functioning, work, illness perceptions, medication beliefs, quality of the partner relationship and social network are also required to optimize treatment [2,62].

Towards evaluation of burden of disease: patient-reported outcome measures

Several measures have been developed and validated for the assessment of HR-QoL in pituitary disorders. Generally, it is recommended that a generic measure (covering general HR-QoL domains) is combined with a disease-specific measure (covering HR- QoL aspects relevant for a specific disease). Disease specific HR-QoL questionnaires are available for acromegaly (ACROQOL) and Cushing's disease (CushingQOL), and a tool is available for growth-hormone deficiency [5,6]. Recent reviews have summarized the available literature on HR-QoL, with general agreement that limitations in HR-QoL in long-term follow-up persist [39,48].

Patients with pituitary disorders usually face a combination of hormone oversecretion, tumour issues and hypopituitarism; therefore, a more generic pituitary questionnaire may be preferable. We recently developed the Leiden Bother and Need Questionnaire for pituitary patients [4]. This questionnaire was developed on the basis of focus groups involving patients with main pituitary conditions [46]. This patient reported outcome measures (PROM) assesses the extent to which patients with pituitary conditions are bothered by certain complaints, as well as the extent to which they feel a need for support from healthcare professionals. Five subscales are included: mood problems, negative illness perceptions, issues in sexual functioning, physical and cognitive complaints, issues in social functioning. As this PROM was developed as a bother and need list, it not only identifies issues but can also help healthcare professionals to address the unmet needs experienced by patients and to refer patients for psychosocial support.

In first long-term follow-up evaluations, fatigue was the main complaint (17%), followed by difficulties in performing work, problems with concentration and sensitivity to stressful situations. Pain was a bother in 10%, exceeding patients' own limits (10%). Sexual and sleeping problems were also present in 10% of patients [4].

When evaluating the need for help, fear of tumour recurrence, help for mood swings and memory were mentioned additionally. This PROM is currently being translated in different languages and will be used in longitudinal studies and in clinical outpatient settings [4].

Practice points

- Pituitary conditions have significant burden for patients owing to the effects of the tumour, hormone overproduction, hypopituitarism and the chronic character of the disease.
- To relieve patient burden, a multidisciplinary team in a centre of excellence should provide personalized medicine, usually with combined interventions and also psychosocial support.
- To measure and evaluate patient burden, further development of PROMs is required, both in research and within a clinical setting.

Research agenda

- Developments of core clinical outcome sets and PROMs to evaluate various therapeutic strategies in time and registries to follow patients.
- Trials to study timing of preventive interventions, and to compare surgical and medical strategies for HR-QOL outcome.
- Improved surgical strategies to preserve gland functioning and optimize complete resection.

Acknowledgments

LBNQ was developed and this was partly supported by an IIR (PINET) of Ipsen.

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