

## Neuroendocrinology

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## **Review**

### **Title: *Patient-centred outcomes with pituitary and parasellar disease***

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Short Title: ***Patient-centered outcomes***

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1 **Abstract**

2 Over the last 2 decades advances in the diagnosis and management of pituitary diseases  
3 have made it possible to attain an endocrine “cure” in a large proportion of patients. In  
4 other words, tumors can be excised or controlled with drugs, and mass effect of the  
5 lesion on surrounding structures be solved, and pituitary deficiencies can be substituted  
6 with all relevant hormones. While this is considered a satisfactory outcome for health  
7 care providers, patients often suffer from an aftermath of prior endocrine dysfunction  
8 exposure, with irreversible effects both physically and psychologically, which have a  
9 great impact on their everyday life. Diagnostic delay, often of several years, adds a  
10 negative impact on health perception. This affects their social, professional and family  
11 domains and determines their future life. Understanding that this may occur is  
12 important and health care providers should offer information to prepare the patient for  
13 this difficult journey, especially in the case of acromegaly, Cushing disease or  
14 hypopituitarism. In order to maintain in the long-term a good quality of life, patients  
15 need to adapt to this new situation, something that may be difficult, since they often  
16 cannot continue with all the activities and rhythm they used to do. Depression is often  
17 the consequence of maladaptation to the new situation, leading to impaired quality of  
18 life.

19

## 20 **Introduction**

21           Quality of life (QoL) does not mean the same for a health care provider (HCP) and  
22 for a patient. An endocrinologist considers pituitary disease to be controlled if pituitary  
23 hormone function is normal and tumour growth is stable; with current surgery and  
24 medical therapy this is possible nowadays in most patients. But patients would like to  
25 perform daily activities as they did prior to suffering from pituitary disease, personally  
26 and professionally, without physical or psychological limitations, pain or social or family  
27 problems related to their disease; if this is not the case, the patient will hardly consider  
28 himself "cured" or experience a good health-related QoL. They want to feel healthy,  
29 independently of what the hormone or imaging results show. These subjective feelings  
30 of health perception of the patient, can be measured with Patient Reported Outcome -  
31 PRO- questionnaires, and are contemplated by administrators and regulating agencies,  
32 when considering health-related decisions, i.e., authorising reimbursement of new  
33 drugs, or devoting health resources to a particular group of patients.

34           Questionnaires are more and more frequently used to evaluate QoL and the long-  
35 term impact on health perception after suffering pituitary dysfunction [1]. It is now  
36 evident that years after "curing" pituitary dysfunction, patients still suffer from more  
37 cardiovascular, skeletal and neuropsychological morbidity (i.e., worse executive  
38 function, emotional coping, leading to anxiety, depression and psychological distress, as  
39 well as memory and cognition complaints), especially after hypercortisolism of  
40 Cushing's syndrome (of either pituitary or adrenal origin, or after exogenous treatment  
41 with high doses of glucocorticoids and/or longterm exposure), acromegaly or  
42 hypopituitarism [2-10]. Patients complain of impaired QoL related to dimensions vital  
43 for daily life, but often ignored by clinicians [3]. Common complaints are physical (poor  
44 stamina, body image, and libido) and emotional (slower on the uptake, anxiety or being  
45 depressive) and less frequently social issues, although visual or other problems, which  
46 prevent driving, do have a great negative impact [1, 2].

47           Working disability (no paid job, need of sick leave, or not being productive while  
48 at work due to difficulties in concentrating and losing the train of thought) is common in  
49 patients with pituitary tumours; furthermore, patients with a paid job experience a  
50 better QoL than those who are unemployed [11]. Patients with a diagnosis of

51 hypopituitarism, acromegaly or Cushing's disease -CD- experience more working  
52 problems than non-functioning pituitary adenomas - NFPA- or Rathke's pouch cysts.  
53 Current use of medical therapy or having undergone radiotherapy impact more  
54 negatively than being controlled after surgery. Higher education and income levels, as  
55 well as being married or with a stable relationship, are also associated with a greater  
56 probability of being employed (11). These persistent limitations after pituitary disease  
57 explain the greater probability of early retirement, shorter working hours or the need of  
58 adapting jobs to persistent limitations, in patients with pituitary disease. Thus, any  
59 initiatives that favour a better adaptation to the current situation will be beneficial not  
60 only for the individual patient, but also for society at large.

61

62

### 63 **Comparison of the impact of different pituitary diseases on patients' health** 64 **perception**

65 As any other chronic health process, pituitary diseases may affect everyday life.  
66 Features like female gender, older age, hypopituitarism, active disease, depressive  
67 symptoms, negative illness perceptions, prior radiotherapy, tumour recurrence and  
68 frequent check-ups negatively affect perceived health and QoL and are common to all  
69 pituitary diseases. Other features that affect QoL are specific to acromegaly, CD or  
70 AGHD, situations where QoL is more impaired than in NFPA or prolactinomas [1, 12-17,  
71 20].

72 The individual patient tends to adapt to perceived limitations, with more or less success.  
73 With a good adaptation, perceived QoL may be quite acceptable despite persistent  
74 morbidity, while maladaptation usually leads to frustration, anxiety or depression and  
75 worse QoL. Educating patients on the nature and consequences of pituitary diseases by  
76 multidisciplinary teams is helpful to understand the nature and adapt to limitations  
77 [21]. The patients' family and social environment can also play a positive role on  
78 patients' outcome, contributing to accept the new situation, by showing understanding,  
79 comprehension, support, and a positive approach to day-to-day life [22].

80 In a pilot study carried out when patients attended their outpatient appointment during  
81 2019, they were asked to describe how their pituitary disease had affected their

82 everyday life (Santos et al, unpublished results). Fifty-four patients were interviewed,  
83 14 patients diagnosed of Cushing's disease, 14 with acromegaly and 14 with a  
84 prolactinoma, and 12 with a non-functioning pituitary adenoma (Table 1).

85 Patients diagnosed with Cushing's disease had the greatest impact of the disease on  
86 their life (7.5 out of a maximum of 10), followed by prolactinoma (6.8), acromegaly (6.5)  
87 and non-functioning adenomas (5.8) (Figure 1 A). In the case of prolactinomas, they  
88 were mostly large macroadenomas, half of which were males with invasive lesions. In  
89 acromegaly, women declared to have experienced a much greater impact than men (8.9  
90 versus 4.2), while clear gender differences were not observed in other diagnostic groups  
91 (Figure 1 B).

92 Emotional complaints in these 54 patients globally were more prevalent at diagnosis,  
93 but were still quite prevalent during the interview at follow-up (Table 2). At diagnosis,  
94 only 18 (33%) recalled to have felt fine, while at follow-up 33 (61%) referred to feel  
95 happy and fine. Thus, despite improvement, more than half still experienced emotional  
96 discomfort including anxiety, depression, sadness, nervousness, mood swings, worry,  
97 fear, lack of initiative, loneliness or dislike of body image after treatment.

98 Social issues at diagnosis and during the interview are globally reported in Table 3. At  
99 diagnosis, 70% did not recall any social issues, while 14 (26%) referred not wanting or  
100 experiencing difficulties in going out for different reasons, physical and psychological.  
101 At follow-up, the situation had improved, since 44 patients (81%) referred no problem.

102

### 103 **Promoting patient empowerment by the health care providers**

104 Perception of outcome after treatment of pituitary disease is often overseen or ignored  
105 by health care providers, unless specifically mentioned. They struggle with QoL issues  
106 not finding any understanding, and feel isolated, lonely and scared, not knowing how to  
107 best manage their perceived declining health into the future. Listening to the  
108 experiences of "cured" patients (individually or through patient associations) are very  
109 illustrative, and deserve more attention than given up to now. For example, patients  
110 often state that they were hardly listened to, and since they were endocrinologically  
111 "cured", their complaints were not considered. This generates anxiety, feeling  
112 bewildered or a hypochondriac. If patients are made aware that some of their perceived

113 problems may be related to the prior diagnosis, it allows them first to recognize a  
114 problem they are experiencing, with a reason and explanation, which they can therefore  
115 try to tackle. This gives them peace of mind, energy and hopes that is often perceived as  
116 therapeutic, with a sense of relief, since they find a confirmation that their feelings are  
117 real and not imaginary.

118 In words of some cured Cushing disease patients, the discussion on how challenging the  
119 recovery may be after the surgery helps normalize an often very difficult journey. Just  
120 knowing that someone understands the physical and psychological devastating  
121 aftermath of chronic high cortisol levels and what they are going through is very  
122 therapeutic, with a feeling of being validated and understood. Furthermore, the  
123 devastating changes induced by hypercortisolism on body image are very distressing, as  
124 illustrated by a young graphic designer who drew herself as she recalled she was prior  
125 to treatment, and 2 years later when her adrenal axis was normal (Figure 2).

126 Education and/or information by devoted and empathic multidisciplinary teams with an  
127 understanding of these persistent issues facilitate an adaptation to these limitations,  
128 making the patients aware that this may occur. Additionally, understanding and a  
129 positive approach to day-to-day life, comprehension and support from family or friends,  
130 contribute to accept this new situation, affecting positively patients' health perception  
131 and long-term prognosis.

132 Patients appreciate that health care providers be patient and encouraging, since they  
133 often cannot grasp all the implications a prior diagnosis of a pituitary disease may have.  
134 It takes time for them to accept the whole situation and adapt to it, especially when they  
135 don't feel "normal and healthy". Most appreciate receiving complete written  
136 information on their diseases and the consequences it may have, although each  
137 individual is unique. Being kind, empathic and listening to the patients to identify  
138 specific issues which can be dealt with is much appreciated and helps them feel better.  
139 For some, contacting other patients through patient associations, forums, Facebook or  
140 social network groups, is very helpful.

141

142 **Conclusion**



143 Patient-centred outcome measures including evaluation of QoL, complement  
144 biochemical and radiological workup of pituitary patients. Health perception is worse in  
145 active disease, especially with hypercortisolism due to Cushing's disease, acromegaly  
146 and hypopituitarism, and is often still impaired, even in the presence of endocrine  
147 "cure". Pre-existing psychopathology like anxiety, depression or an irritable mood  
148 further worsen QoL, while adaptation to the new physical, psychological or social  
149 limitations are associated with better health perception and QoL. Identification of  
150 persistent anxiety and depression, for example with a simple and easily accessible  
151 questionnaire like HADS (Hospital Anxiety and Depression Scale) can classify those  
152 individuals who may benefit from psychological or psychiatric help to overcome their  
153 problem. A supportive social or family environment can also be helpful, and can be  
154 favoured by informing and educating the patients and their environment on the nature  
155 of their pituitary disease and what to expect after so-called successful treatment.

156

157 **Statements**

158 **Disclosure Statement**

159

160 The senior author (SMW) is the co-author and co-owner of the copyright the disease-  
161 specific quality of life questionnaires AcroQoL and CushingQoL, as illustrated in the  
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167

168 **Author Contributions**

169 SM Webb has written this review. All authors have contributed with data included in  
170 this review, as well as have performed critical reading, approval of the final version and  
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## **Figure Legends**

Figure 1 : A) Patient's subjective impression on the impact of different pituitary diseases on everyday life (maximum impact 10, minimum 0). B) Women with acromegaly refer a much greater impact of their disease than men, while this sexual dimorphism was not observed in other diseases.

Abbreviations CD: Cushing disease; ACR: acromegaly; PRL: prolactinoma; NF: Non-functioning adenomas

Fig. 2. A) Subjective impression of body image while actively cushingoid and B) 2 years after successful surgery, as drawn by a 20-year old graphic designer.



Table 1: Physical impact referred by the patients at diagnosis and during the recent interview, in the different pituitary diseases

**Cushing disease (n=14, 3 males; age 27- 75 years; 1 on cortisol-lowering drugs; substitution therapy: 3 growth hormone; 8 L-thyroxine; 3 hydrocortisone; 1 testosterone)**

At diagnosis	During interview:
Swollen (7)	Feeling fine (5)
Increased weight (5)	Feeling tired (6)
Excessive fatigability (3)	Would prefer to be thinner/less swollen (3)
Body shape (3)	Pain (2)
Hirsutism (3)	More visceral fat
Bruising (3)	Heart/walking problems
Pain (2)	Sleeping difficulties
Sleeping difficulties (2)	Curly hair (after radiotherapy) (2)
Menstrual irregularities (2)	Feeling very cold
	Desire of plastic surgery to recover body image

**Acromegaly (n=14, 7 males; age 35- 66 years; 3 on GH-lowering drugs; substitution therapy: 4 growth hormone; 5 L-thyroxine; 4 hydrocortisone; 3 testosterone)**

At diagnosis	During interview:
Ok, minor changes perceived(3)	Feeling fine (3)
Changes in facial features (3)	Pain (7)
Increase in size of hands and feet (2)	Cannot recognize myself in the mirror
Feeling tired (2)	Feeling tired
Too tall (2)	Abdominal discomfort with oral medication
Pain (2)	Desire of plastic surgery to recover body image
Swollen (2)	
Loss of vision	

**Prolactinomas (n=14, 8 males; age 27- 61 years; 11 on prolactin-lowering drugs; substitution therapy: 1 growth hormone; 4 L-thyroxine; 3 hydrocortisone; 2 testosterone)**

At diagnosis	During interview:
Headache (6)	Feeling fine (7)
Menstrual irregularities (5)	Loss of vision (2)
Loss of vision (5)	Feeling tired (2)
Low sexual desire (4)	Desire of plastic surgery to recover body image
Feeling tired (2)	Substitution therapy is imperfect
Galactorrhea (2)	
Increase in breast size (3; 2 ♂)	
Swollen and increased weight (2)	
Pain	
Sterility	

**Non-functioning adenomas (n=12, 8 males; age 33- 78 years; substitution therapy: 3 growth hormone; 4 L-thyroxine; 4 hydrocortisone; 5 testosterone)**

At diagnosis	During interview:
Feeling fine	Feeling fine (6)
Headache (8)	Walking problems (2)
Loss of vision (5)	Low energy
Dizziness (2)	No libido
Pain (2)	Loss of vision
Vomiting (2)	Feeling tired
Feeling tired	
Nausea	
Impotence, no ejaculation	

Table 2: Emotional complaints at diagnosis and during the interview (all 54 patients together, Cushing disease, acromegaly, prolactinoma and non-functioning adenoma)

<b>At diagnosis</b>	<b>During interview:</b>
Feeling fine (18)	Feeling fine (30)
Depression (7) / Sadness (5)	Happy (3)
Fear (5)	Do not feel like doing anything (2)
Mood swings (4)	Nervousness / Anxiety (3)
Irritability (3) / Anger (2)	Dislike of my body (3)
Apathy (2)	Sadness / Depression (5)
Anguish (2)	Mood swings (3)
Nervousness (2) / Anxiety	Worried about medical controls (2)
Difficulty concentrating	Fear (2)
Feeling worried	Feeling lonely
Low self-esteem	

Table 3: Social issues at diagnosis and during the interview (all 54 patients together, Cushing disease, acromegaly, prolactinoma and non-functioning adenoma)

<b>At diagnosis</b>	<b>During interview:</b>
No impact (38)	No problems (44)
Problems with family/partner (2)	Often go out with family and friends (4)
Did not want to go out (3)	Going out less (3)
Going out less (11) <ul style="list-style-type: none"> <li>- Only as an obligation (3)</li> <li>- Only when others proposed it (2)</li> <li>- Due to my physical appearance (4)</li> <li>- Due to difficulties walking</li> <li>- Because feeling unwell</li> </ul>	Do not want to go out, it involves too much effort (2) No sexual desire, leading to problems with partner

Figure 1 A)

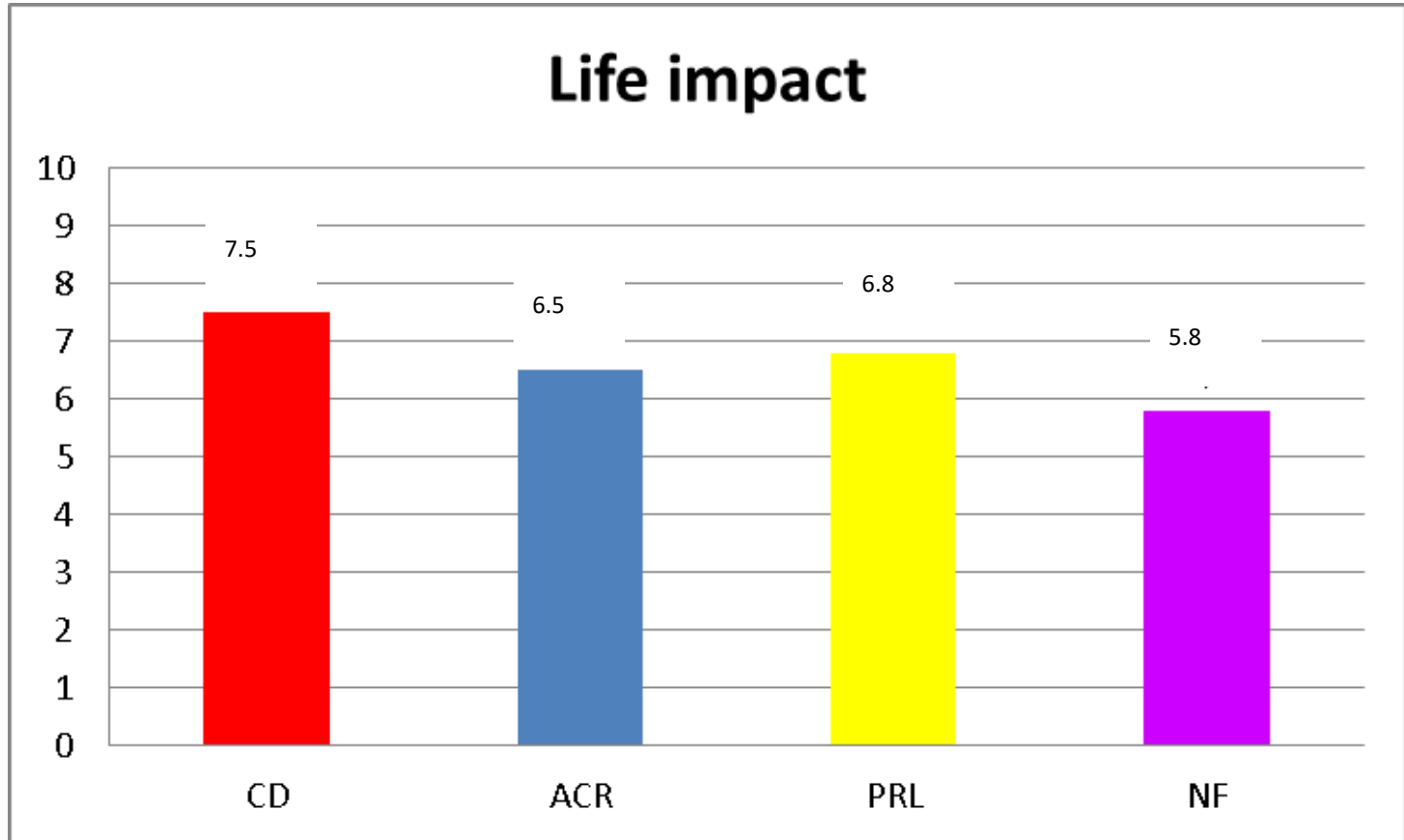


Figure 1 B)

