Conducting pituitary care: innovation and standardization in a rare disease

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13 General discussion and summary

GENERAL DISCUSSION

This thesis outlines an effort to standardise management and outcome measurement in the rare disease field of pituitary tumours. Moreover, it is an effort to improve patient-centred care in this field.

Nowadays, most clinicians aim to provide care via the principle of evidence based medicine. The aim of evidence based medicine is treating patients with treatments that have been proven by scientific evidence to yield the best results. Scientific evidence can be graded from most to least reliable using different levels. The meta-analysis, a summary and reassessment, of well-performed randomized controlled trials is considered as the highest level of scientific evidence (level I), followed by a single well-performed randomized controlled trial (level II). This practice has yielded great improvements in outcomes in common diseases, such as diabetes mellitus or various oncologic diseases. Initially, most evidence was gathered on clinician-reported outcomes: outcomes of treatment that physicians consider to be relevant. In recent studies evidence is gathered on patient-reported outcomes as well, such as quality of life and perceived burden of disease. Positive clinician reported outcomes do not always correlate with patient-reported outcomes and analyses of both are necessary to provide high quality care. With good quality of evidence, most preferably also on specific subgroups of patients, personalized, tailor-made evidence based medicine can be provided.

However, providing evidence based medicine in the field of rare diseases is more challenging. To perform randomized controlled trials with sufficient statistical power to capture significant effects, large patient samples are necessary. As patient numbers are limited, so are good quality scientific data; randomised controlled trials with large sample sizes, and consequently meta-analyses, are sparse. Therefore, rare diseases are often confronted with treatments based on lower quality evidence such as retrospective cohort studies and expert opinions. Though every rare disease on its own is uncommon, it is not rare to have a rare disease. Over 1 million Dutch citizens (>5%) have a rare disease. Therefore, these scientific shortcomings have an important impact on the lives of a substantial proportion of the population.

This chapter will discuss how the negative effects can be limited, what efforts have been made, and what positive effects future interventions can yield.

CENTRAL PRINCIPLES OF VALUE-BASED HEALTHCARE: AIMING FOR PATIENT-CENTRED CARE AND OUTCOME MEASUREMENTS AND IMPROVING VALUE

To truly improve value of care, a number of prerequisites have to be fulfilled. First of all, the healthcare provider must have a clear vision of what the care process looks like. Which patients and diseases are regarded as the population, what procedures are provided and what is the duration of this process; the care pathway. When this is established, value of these procedures can be measured by assessing the effect on outcomes, preferably patient-reported outcomes, such as health-related quality of life [1, 2]. Finally, an assessment of cost of the provided procedures should be made. In order to provide care with the highest value, procedures with positive effects should be implemented or continued and (expensive) procedures with no, or very limited, positive effects for the patient should be abandoned or reduced. In recent years pioneering efforts in implementing Value-Based Healthcare (VBHC) in pituitary healthcare have been made, with studies reporting health-related quality of life following pituitary surgery for various subgroups and studies measuring costs of provided care [3-5].

Improving value for the individual patient can also be achieved by taking into account individual treatment goals and expectations [6, 7]. When clinicians are aware of these goals and expectations, treatment options and counselling can be tailored accordingly through a process of shared decision making. In pituitary tumours symptom remission through surgery alone may not always be realistic, e.g. in case of carotid artery encasement. However, a patient may still opt for surgery with the aim to facilitate medical therapy to a more tolerable dosage or alleviate specific complaints.

It may be utopic to continuously assess changes in patient-reported outcome measures for every procedure, however, studies assessing which measurable determinants influence quality of life across varying procedures are a giant leap in the right direction. With these determinants, patient-centred outcomes can be registered and assessed in aid to improve provided care. In pituitary care, presence of hormone excess or tumour remission and hypopituitarism have both been described as determinants of quality of life [5, 8, 9]. In pituitary surgery, the surgeon always has to find the balance between attempting for complete adenoma resection and prevention of complications. Therefore, the balance between symptom removal and long-term hypopituitarism is a major determinant outcome for patients quality of life. In **Chapter 2 and 3** we report surgical outcomes and complications both separately, and additionally in an integrated outcome classification taking this risk/benefit balance into account . Limited results indicate that

this integrated outcome classification indeed correlates with health-related quality of life, but, more studies with larger samples sizes are needed to confirm our findings..

Moreover, we integrated the achievement of the preoperative goal of surgery. These outcomes are still clinician-reported, yet attempts towards more patient-centred approached, such as for the patient the achievement of the preoperative goal of restoration of visual function, may be more important than gross total resection of the tumour. The integrated outcome was first intended to support a critical analysis of surgical outcomes over time and to analyse the effect of adjustments. The classification has enabled us to detect an increasing proportion of patients with symptom remission including achieved surgical objective without long-term complications over time. In the studied period multiple adjustments have been made to the pathway and surgical volume has increased, therefore, firm conclusions on the cause of this particular improvement cannot be made. The integrated outcomes are now recorded for every patient that underwent pituitary surgery prospectively in our facility in order to facilitate assessment of the effect of care adjustments in the future.

There is also a possible utilisation of the integrated outcome squares in pre-operative counselling. As the new classification also includes the achievement of pre-operative set treatment goals and the occurrence of long-term complications. With results reported according to these aims, preoperative expectation management and counselling is enabled. Treatment efficacy and safety are made insightful to the patient per aim, therefore, they can make a more informed decision on whether or not surgery is preferred over conservative treatment and to what extent the surgeon should strive for total resection. A visual representation can make outcome data most insightful for patients. Integrated outcomes are flexible with respect to definitions, so in future evaluation the PROMs can be included in the definition of intended effect and adverse effect.

PERIODICAL ANALYSES OF THE QUALITY OF PROVIDED CARE: LOOKING FOR WAYS TO IMPROVE

In general, healthcare providers should periodically assess care processes [2]. During some process analyses, absence of protocols or guidelines can become apparent. One of the most common postoperative complications following pituitary surgery is diabetes insipidus (vasopressin deficiency). However, no guidelines were available for clinicians to aid them in the diagnostics and treatment of this complication and how to score them in a complication registry. This resulted in large differences in the post-surgical approach of the patient with symptoms suggesting diabetes insipidus. Some doctors

would immediately start medication, while others would first perform additional diagnostic procedures, which influenced the complication rate. We aimed to standardize the care process to be able to analyse and adjust it as to be most effective and patient friendly. One of the first necessities is to establish diagnostic criteria for this complication as a feasible golden standard test is lacking. **Chapter 4**, proposes a clear definition of postoperative diabetes insipidus (polyuria with low urine specific weigh and hyperosmolality/hypernatremia or unquenchable thirst). Future consensus discussion with (international) experts in the field should hopefully result in a broader adaptation in clinical treatment and outcome reports, as it could enable outcome comparability and incorporation of outcomes between centres. Moreover, Chapter 4 proposes a pathophysiology-based clinical tool to aid physicians with the clinical decision making process, in order to reduce treatment variation.

Additionally, with process assessment some routinely provided procedures could be reduced as no added value of the procedure is seen. In **Chapter 5**, we critically assess the added value of such a procedure: testing residual cortisol secretion using CRH stimulation, a ' habit' in our hospital. When assessing the possible presence of postoperative secondary adrenal insufficiency the performance of the CRH-test showed no added value when compared with a single basal early morning cortisol measurement. This can significantly reduce costs of postoperative care as the CRH-test is a relatively expensive procedure and CRH is prone to drug shortages. Accordingly, we adjusted care by relying on morning cortisol sample and clinical observation, taking into account that HPA-axis evaluation cannot be performed reliably during active diabetes insipidus/SIADH and stressful situations. The analysis of this particular test should not stand on its own and the added value of other (expensive) standard procedures should be analysed as well to reduce unnecessary costs in the care trajectory of pituitary tumour treatment.

Preventing treatment delay and resulting harm is another way value can be improved and unnecessary costs reduced. During an additional analysis of the diagnostic process of optic chiasm compression we found a number of misdiagnosed patients who consequently had a long treatment delay. Therefore, we also analysed these cases with the aim of finding clinical signs to distinguish diseases causing visual field deficit and minimize treatment delay with resulting visual deterioration (**Chapter 6**). This should decrease the need for emergency surgery and persisting visual symptoms and, thereby, improve quality of life.

However, aside from evaluation of existing processes in pituitary tumour care, novel diagnostic procedures might add value too. Therefore, it might be useful to analyse relatively inexpensive diagnostic or prognostic tests and treatment modalities from other disease

fields. Examples include the introduction of the endoscope for skull base surgery after the presentation of good results in sinonasal surgery [10] or self-management interventions for patients with chronic diseases [11], which have been adjusted and applied in various disease groups including neuroendocrinological diseases. In the field of oncology , prognostic value was demonstrated for pre-operative serum inflammation-based scores. In **Chapter 7**, an analysis of these easily measurable biochemical markers of inflammation in pituitary tumours is described. Some of these scores show correlation with treatment outcome in a limited sample. Therefore, the added value of these scores for prognosis and patient counselling may be promising and should be assessed in larger and preferably prospective studies.

HEALTHCARE ORGANIZATION: CENTRALIZATION AND ESTABLISHMENT OF CROSS-BORDER NETWORKS

In the care for rare diseases, because of the complexity of the conditions that do not fit into standard concepts of care, it has now generally been accepted that some form of centralisation is mandatory. Centralisation will increase experience with the required specific diagnostic and therapeutic procedures for a particular rare condition. Clinicians frequently encounter knowledge gaps and areas in which efficiency can be improved. With increasing patient numbers, the experience increases and more clinical data can be gathered to gain and validate new insights. Moreover, this also enables clinicians in tertiary referral centers to further specialize in a rare disease or even a specific part of the diagnostic and/or therapeutic procedure of the care process. With the establishment of specialized multidisciplinary teams, care can be improved and tailored towards the individual needs and an optimal environment can be established for care provision [2].

Another way to improve healthcare for rare disease patients is through knowledge generation by improving (inter)national collaboration between specialists. With increasing centralisation it may be tempting for specialist centres to provide care following their own traditions and beliefs, based on expert opinion because data from (randomized) controlled trials and evidence based guidelines are hardly available. Therefore, collaboration with other specialist centres within specialized networks is warranted. This can be established through collaboration, e.g. through professional societies or associations, or through networks initiated by the European Commission based on the EU Directive of patient's rights in cross-border health are that has been adopted by all EU member states, and led to the development and installation of the European Reference Networks for rare and/or complex conditions (ERNs). Another initiative that arose from the pituitary field was the establishment of criteria for Pituitary Centres of Excellence [12].

Through long-lasting discussions between experts under the auspices of the Pituitary Society from a multitude of countries and multiple disciplines differing insights on what is necessary to provide pituitary care to the highest standards were gathered and compiled into this new consensus proposal. None of the involved clinicians will have provided care according to all the criteria beforehand and hopefully many will be able to apply at least some of these criteria to their facility to improve it. The establishment of ERNs by the European Commission resulted in a total of 24 networks with the aim to reduce present health care inequalities across the EU and cover expertise for all rare and or complex diseases, with Endo-ERN for the rare endocrine conditions. As mentioned, the primary aims of these new rare disease network are first of all to reduce present health inaequalities via improved collaboration between expert clinicians. It also aims to improve patient representation in all processes of healthcare organisation, as well as in educational activities, and registry activities. This is ensured through participation of patient representatives throughout all layers of the network, including the governance structure (co-chair function). As such, these chairs provide a balanced representation of the patient community in decision making within the network and can suggest interventions or investigations to improve patient involvement. Such an investigation with Endo-ERN was a EU wide survey developed to capture patient needs to prioritise and suggest research topics for rare endocrine conditions (**Chapter 9**). Endo-ERN also aims to coordinate and support international research projects in an effort to gain high quality evidence.

USE OF UNIFORM DEFINITIONS THROUGHOUT THE DISEASE FIELD AND LITERATURE

When comparing data and outcomes of various healthcare providers it is mandatory that uniform definitions are used. When uniform definitions are not available, this inevitably will result in large variations in reported prevalence and impaired pattern recognition and analysis. As a result, the ability to draw conclusions from, and therefore, value of registries may be diminished. Moreover, comparability between studies is impaired. Though this may seem obvious, these definitions are lacking for many outcomes and variables in rare disease fields, such as how en when to define the occurrence of postoperative diabetes insipidus after pituitary surgery, even though this is one of the most reported surgical complications (**Chapter 4**). Consequently, efforts should be made to provide these definitions and implement these in the international field. Optimally, definitions should be based on solid pathophysiological grounds, available scientific literature, or if these are not readily available, through expert discussion. The importance of clear definitions is also applicable when measuring performance of healthcare providers. When

different definitions are used for complications or procedures, large variations will occur, not necessarily representing an actual difference in provided care (**Chapter 8**). International expert networks, like Endo-ERN, and specialist associations should take a leading role in the establishment of these definitions, like they already do in the development of clinical practice guidelines guideline- conformity use. They are able to bring disease experts together and stimulate discussions in international meetings and conventions. This can limit unnecessary treatment inequalities between health care providers and countries in the future.

PROSPECTIVE OUTCOME MEASUREMENT AND REGISTRATION

As it is difficult to perform large scale prospective studies, a large proportion of evidence in the rare-disease field is derived from retrospective cohort studies. This type of studies have inherent shortcomings; they can only determine correlation, not causation, need large sample sizes to identify rare events, and are prone to missing date, misclassification, convenience sampling, and inability to adequately adjust for confounding. Some of these shortcomings can be corrected through prospective measurements and registrations. Through expert discussion and analysis of available literature, a set of parameters including patient and disease characteristics, interventions, complications, outcomes, and patient satisfaction can be compiled: the core outcome set. These parameters should be valuable for clinical care as well as for scientific purposes, and should preferably incorporate patient-centred or -reported outcomes (**Chapters 2 and 3**). These parameters should be prospectively registered for all patients to enable a comprehensive overview of a patient group or disease. One of the challenges is to incorporate this in clinical care without creating a burden for patients or clinicians. This can be accomplished by incorporation of automatic checklists in the electronic patient file. In the LUMC such checklists were developed for set time points in the pituitary care pathway and are registered by the treating physician. This development results in more complete and uniform registration, however, a large investment of time and resources from clinicians, researchers, and the IT-department is required to create a coordinated, well-functioning application. At present, there are efforts to create these core outcome sets through (inter)national consensus to allow for large (inter)national registries with reliable, comparable data. This is now possible with the European Registries that serve the ERNs, and in specific EuRRECa, the European Registry for Rare Endocrine Conditions. (ref) As such, registries provide a platform to link care to research and act as platform for quality Improvement and clinical benchmarking. [13-15]. When multiple care provid-

ers use the same outcome sets, formats, experience, and possible adjustments can be shared throughout the field to limit the initial burdens for implementation.

At the national level, In the Netherlands, core outcome sets are being developed for many oncological diseases. Moreover, the professional association of neurosurgeons has implemented a quality registration system that aims to capture predetermined outcomes of every surgically treated patient in the studied fields in 2014. However, data collection and comparison is limited as centres should also protect its patients' privacy and data. First results on between-hospital variation in outcomes of glioblastoma surgery have been published and show large variations between centres [16, 17]. The source of these variations should be studied. They may result from differences in case mix, but also from treatment variations that may result in improved care if implemented in other centres. First results of pituitary surgery are yet to be reported, but may yield novel insights. In the future, these registrations should also include measurements of health-related quality of life. Such registrations enable comparisons between centres with differing treatment ideologies regarding pituitary tumour care, such as more primarily medical and more surgically oriented approach, or centres with differing patient volumes. However, due to the aforementioned difference in case mix, especially between second and third-line treatment facilities, interpretation of these variations should always be made with caution.

CONCLUSION

It is challenging to providing evidence-based or value-based healthcare in rare diseases. However, as a substantial part of the population is affected by a rare disease and the population is getting older. The societal impact of having a rare disease is significant, and therefore it is mandatory to overcome these challenges to provide high quality and affordable care also to rare disease patients. Meticulous and preferably continuous assessment of treatment outcomes and its effect on the patients' quality of life aid in determining which procedures truly add value and which procedures do not, and can therefore be omitted. Results can be presented in Outcome Squares to aid analysis of process alterations. This way of outcome presentation incorporates the difficult balance between efficacy and safety. In addition, large studies could be performed to get insight on the determinants of quality of life and study these outcomes. In rare diseases some form of centralisation of care and international collaboration are necessary to reach adequate sample sizes to make reliable assessments. Cross-border rare disease networks and professional associations should take a lead in these effects, like establishing uniform definitions of outcomes for better comparability of results, establishment of prospective international registries and coordinating scientific efforts.

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