European Registery of Cushing's syndrome (ERCUSYN)

Introduction

Cushing's syndrome is a rare endocrine disease due to chronic exposure to hypercortisolism, both exogenous and endogenous. The diagnosis is often delayed and untreated Cushing's syndrome has a 50% five year mortality, but "successful' control of hypercortisolism reduces, but does not eliminate, the long term morbidity. Recently persistent central obesity, cardiovascular risk, abnormal body composition and impaired quality of life have been shown to persist for more than 10 years despite with remission of hypercortisolism. The perception of an unmet need in the diagnosis and management of patients with Cushing's syndrome formed the basis of an application to the EC under the Public Health Program, the aims of which included:

- To improve the care and outcomes of Cushing's syndrome in Europe
- To identify the reasons for the delay in diagnosis, and establish optimal, cost-effective diagnostic investigation, and therapy (surgery, radiotherapy, medical treatment) and define end points of treatment (biochemistry and quality of life)
- Better appreciation of the long term impact on mental health and quality of life
- Analysis of the regional differences in management with a view to disseminating best practice.

Current achievments

The ERCUSYN (European Registry on Cushing's syndrome) data and database are owned by the European Society of Endocrinology (ESE). The ERCUSYN project has had from its inception the ESE as an associated partner. It was funded by the European Commission for 3 years (2007-2010). Patient entry into the registry opened Sept 2008 and a webpage (www.ercusyn.eu) has been constructed by the founding partners with specialist assistance from Lohmann & Birkner GMBH (Berlin), who were also an associated partner of ERCUSYN.

The ERCUSYN webpage offers brochures for patients and primary care physicians in different languages. It also contains a map with details on the currently 36 participating centres in 23 European countries which patients may use to identify centres of excellence. ERCUSYN has thus effectively formed a network among European centres of excellence in pituitary/adrenal endocrinology, which now can serve and function as terminals or web-nodes to recruit further endocrine centres from their respective European countries.

The database permits patients diagnosed since 2008 to be entered or retrospective cases diagnosed since 2005 if an annual update can be provided. In October 2010 an initial analysis included data on 509 patients, of which 481 had a complete dataset. Abstracts on different aspects of this initial analysis have been recently submitted to the ECE2011 (Rotterdam) and ENDO2011(Boston). Some of the highlights include the following:

- There is a long delay between onset of symptoms and diagnosis (2.9 $\pm$ 3.7 yrs; range 0 - 22, median 2 yrs)
- Mean age at diagnosis is 44±14 years, with a female predominance, as expected (390 females vs. 91 males)
- The ERCUSYN project allows an analysis of the heterogeneous clinical presentation. When patients were divided into 4 major etiologic groups:

pituitary-dependent Cushing's syndrome (CS) (PIT) (66%), adrenal-dependent CS (ADR) (27%), CS from an ectopic source (ECT) (5%) and CS from other etiologies (OTH) (2%), several differences were seen, i.e., in ECT males are more prevalent compared to the other groups (46% vs 14-20%, $p<0.01$). The ADR group was significantly older than the PIT group (46.9±13.6 vs. 42.7±13.5, $p<0.05$). ECT patients had a higher baseline prevalence of hirsutism compared to the global values (92% vs 60%) and diabetes (74% vs. 38%). Skin alterations (78%), menstrual irregularities (63%) and hirsutism (63%) were more prevalent in PIT than in ADR ($p<0.01$). When both sexes were compared, reduced libido was more prevalent in men (60% vs. 40%; $p<0.01$), as well as vertebral osteoporosis (40% vs. 20%; $p<0.05$), and vertebral (52% vs. 18%; $p<0.001$) and rib fractures (34% vs. 23%; $p<0.05$).

- Initial symptoms often determined the specialist first consulted, which often missed the correct underlying diagnosis: ECT patients more frequently initially consulted a diabetologist, while gynecologists were consulted for initial complaints of CS more by women with PIT-CS or ADR-CS than with ECT-CS group ($p<0.05$). Overall, weight gain resulted significantly more common in women than men ($p<0.01$).
- Baseline Quality of Life (QoL) evaluated by generic (EuroQoL) and disease-generated (CushingQoL) questionnaires were available in 27% of the patients, and disclosed significantly lower scores of Visual Analogue Score (VAS) of the EuroQoL (when compared to reference values from France and Spain), as well as significantly impaired QoL judged by CushingQoL.

In Conclusion, at this initial stage, the ERCUSYN project is starting to generate useful data answering the questions for which it was created. The results presented above illustrate differences in clinical presentation depending on gender and etiology, confirms a long delay between onset of symptoms and diagnosis of CS, with a high number of specialists consulted who often missed the correct diagnosis. Furthermore, morbidity at diagnosis is high, with low bone mass, especially in men, and impaired QoL. Less than half the cohort was actively working, which is surprising in a cohort of patients with a mean age of 44 yrs. Thus, there is great potential for improvements in the time to diagnosis which would have obvious consequences for patients and for the health care systems that must meet the long term sequellae of delayed diagnosis.

ERCUSYN represents the largest collaboration of endocrine centres in Europe and has potential not only for improving the care of patients with Cushing's syndrome, but also to extend its collaboration into new areas. The ESE may use this network to disseminate information and encourage further interaction between endocrinologists across Europe.