Épidémiologie et « follow-up » de la maladie de Cushing

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L’épidémiologie de la maladie de Cushing (MC) est peu connue car on ne dispose pas d’études systématiques à ce propos. Nous avons récemment rapporté notre expérience sur l’analyse de 300 cas environ de syndrome de Cushing recueillis dans une étude multicentrique italienne. Le nombre de patients avec MC récemment diagnostiqué a sensiblement augmenté dans les dernières années (7,4 ± 0,71 pts/année avant 1987 et 26,4 ± 4,12 pts/année après 1987), probablement en raison d’une augmentation de la connaissance de cette maladie et de la disponibilité de techniques diagnostiques. L’élévation du cortisol libre urinaire (CLU) est plus importante chez les hommes que chez les femmes et le CLU apparaît négativement corrélé avec le délai entre l’apparition des premiers symptômes et le diagnostic. Pour reconnaître la MC parmi tous les patients avec diabète, obésité et hypertension artérielle il est nécessaire d’effectuer des épreuves de screening fortes sensibles [par exemple, le CLU, la cortisolémie à minuit, le freinage faible (1 mg) par dexaméthasone] qui peuvent toutefois donner de faux positifs. Dans ces cas, le test au CRH précédé par dexaméthasone ou bien le test à la desmopressine peuvent différencier la MC des pseudosynonymes de Cushing. La différence entre la prévalence de la MC et celle de la sécrétion paranéoplasique de ACTH (SPA) diminue la précision diagnostique des tests utilisés pour la démarche diagnostique entre ces deux étiologies (test au CRH, freinage lors du test à la dexaméthasone à dosage élevé, cathétérisme bilatéral des sinus pétreux inférieurs). Il faut donc étudier des épreuves diagnostiques pour reconnaître la SPA plutôt que la MC. La chirurgie hypophysaire par voie transphénoïdale a été proposée en première intention entraînant une rémission de l’hypercortisolisme dans 70 % des cas environ avec un rechute de 15 % dans les 10 ans. La définition de la rémission postopératoire et du risque de rechute cependant est variable selon les séries et un suivi de cas sur plusieurs années est nécessaire pour en définir la validité. La plupart des symptômes de l’hypercortisolisme ont disparu après rémission bien que quelques conséquences cardio-vasculaires de longue durée aient été observées. Enfin, conformément à d’autres études, la mortalité des patients guéris de MC est comparable à celle de la population générale.


Epidemiology and follow-up of Cushing’s disease

Little is known on the epidemiology of Cushing’s disease (CD) as relevant data on such a rare disease can only be obtained from large-scale studies. We addressed this topic analyzing the data obtained in the Italian multicenter study which comprised nearly 300 patients with CD. The number of newly diagnosed patients with CD increased markedly in the second decade of the study (from 7.4 ± 0.71 pts/year prior to 1987 to 26.4 ± 4.12 after 1987) probably reflecting the

The literature dealing with the epidemiology of Cushing disease (CD) is definitely meager. Data of epidemiological relevance on a rare disease such as CD can in fact be deduced only from large-scale studies and past estimates of incidence and prevalence of CD are essentially referred from a single publication [5]. We have recently concluded a multicenter study on CD and collected, among the nearly 500 patients with Cushing’s syndrome (CS) of various etiology, 288 patients with CD [13]. This vast database made it possible for us to provide additional information on this issue.

Reportedly, CD has an estimated incidence of 5-6 per million inhabitants per year [5] although this estimate should be lowered to 2.4 per million per year according to a recent study carried out in Spain [11]. CD is a second-line diagnosis as it must be differentiated from other causes of endogenous hypercortisolism thus the incidence of these diseases must also be taken into account. Malignant and benign cortisol-secreting adrenal tumors have an estimated incidence close to 4 per million per year [21] although in selected populations, such as the Japanese, incidence of adrenal adenomas is much higher [10]. Ectopic ACTH secretion (ES) is known to be diagnosed approximately four times less than CD but this figure is probably underestimated as hypercortiso-
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Epidemiology and follow-up of Cushing’s disease

Clinical presentation of CD is well known and the percentage of signs and symptoms reported by other big series [25, 28] tallies with the results obtained in our patient population. The clinical picture of CD was, on average, milder than the one observed in AC and ES; indeed, hypertension, muscle atrophy, bruisability, overt diabetes, hypokaliemia and hypercalcemia were more frequent in the latter two etiologies. Menstrual changes were registered in slightly more than half of female patients with CD, which is a somewhat lower frequency than previously reported [25, 28]. Of interest, hyperprolactinemia was recorded in 9 % of patients with CD but was not more frequent among oligo-amenorrheic women. Worth mentioning may also be the high prevalence of thyroid nodules (around 60 %) which we observed in a study comprising 25 patients with CD [12]. Among other endocrine derangements, diabetes and osteoporosis are classical components of the clinical picture but a few cases of CD presenting as poorly controlled diabetes mellitus in obese patients or severe osteoporosis have been described [16, 22]. More unusual presentations of CD are spontaneous rupture of the Achilles tendon, a vascular necrosis of the hip or head of femur, open angle glaucoma, hepatic steatosis, recurrent thromboembolic events, cutaneous alternariosis and spinal epidural lipomatosis which alert us to the fact that CD may come under unexpected guises.

Again relevant to epidemiology, the recognition of a low incidence disease such as CD amid the abundance of obese, hypertensive and diabetic subjects requires tests with distinctly high sensitivity. Currently available heightened awareness of the disease and the increased availability of diagnostic tools. Urinary free cortisol (UFC) levels were significantly higher in men than in women and were inversely correlated with the time interval between appearance of symptoms and diagnosis. Recognition of CD among patients presenting with common diseases such as obesity, diabetes and hypertension requires highly sensitive screening tests (e.g. UFC, midnight cortisol in saliva, overnight dexamethasone suppression test) which however may yield false positive results. In doubt, second line testing using dex-CRH or desmopressin may distinguish between CD and pseudoCushing. The different prevalence of CD and ectopic ACTH secretion (ES) undermines the diagnostic accuracy of tests used for the differential diagnosis of ACTH-dependent Cushing’s syndrome (i.e. CRH, high dose dexamethasone, IPSS). Tests aimed at identifying ES rather than CD are needed to overcome this bias. Transphenoidal surgery was the preferred choice of treatment for patients with CD, resulting in remission in 70 % operated patients with a 15 % relapse rate over 10 years follow-up. Definition of remission after surgery and parameters predictive of relapse, however, vary according to studies and long-term follow-up is required to establish their validity. Most clinical manifestations of hypercortisolism disappeared after remission although some long-lasting effects on the cardiovascular system had been observed. Finally, according to recent reports, mortality rates for patients cured of CD appear comparable to those of the general population.

The data collected through our study, which involved most major Italian endocrinology centers, allows several conclusions to be drawn on the epidemiology of CD in Italy. The study encompassed patients diagnosed from 1975 to 1995 and it was readily apparent that the number of newly diagnosed patients increased markedly starting from the later half of the 1980s. Indeed, the number of diagnoses prior to 1987 averaged 7 per year, whereas a three-fold higher incidence of CD was recorded from 1987 to 1995 (table I). This same trend was observed also among patients with other etiologies of CS (see Table I). This increased detection may be partly accounted for by a heightened awareness of the disease, a more widespread availability of sophisticated diagnostic tools and the establishment of endocrinology referral centres which allowed previously scattered patients to be gathered. In agreement with the known gender distribution, CD was approximately five times more common in women than in men. Interestingly, urinary free cortisol (UFC) levels were higher in men than in women (434.1 ± 51.96 % vs 342.1 ± 21.01 % of the upper limit of the normal range, respectively, p < 0.01) suggesting that hypercortisolism is more pronounced in males at the time of diagnosis. As regards the age at diagnosis, CD was detected mostly between 25 and 45 years of age; a similar age distribution pattern was observed also among benign adrenal tumors (AA) whereas adrenal carcinoma (AC) and ES presented an apparent bimodal distribution with marked preponderance of patients diagnosed in childhood/adolescence and again later in adult life (fig. 1). Indeed, the highest incidence of ES was observed at an older age compared to all other causes of CS. However, this does not imply that ES is the most frequent cause of CS among senior patients since CD still remains the most frequent etiology of CS in patients over 55 years of age.

In our series, the time interval elapsed between the appearance of the first symptoms and the clinical recognition of CD was on average slightly over two years. The time-to-diagnosis interval was negatively correlated with the degree of hypercortisolism as this interval was shorter in patients with higher UFC (r = – 0.2, p < 0.01). This pattern can be extended to the other etiologies of CS as AC and ES, the two etiologies characterized by highest UFC levels, presented a shorter time-to-diagnosis (13 months and 18 months, respectively).

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Again relevant to epidemiology, the recognition of a low incidence disease such as CD amid the abundance of obese, hypertensive and diabetic subjects requires tests with distinctly high sensitivity. Currently available
screening tests for hypercortisolism include measurement of UFC and evaluation of cortisol inhibition after low dose dexamethasone and cortisol circadian rhythm. Of the three, UFC is the more sensitive given the fact that virtually all patients with CD display elevated UFC levels; multiple urine collections, however, must be performed as we and others have registered normal UFC values in a single urine specimen in some 10% of patients with CD [13, 20]. Cortisol circadian rhythm can also be established, in our experience, by measurement of free cortisol levels in saliva collected at midnight, a viable alternative to cortisol measurement in plasma which obviates the need for hospitalisation. These tests, although all highly sensitive for the detection of a low prevalence disease such as CD, are burdened by a not equally high specificity [8, 19]. For those patients in whom the diagnosis of CS remains doubtful the dexamethasone-CRH test [29] or stimulation with desmopressin [17] may be resolutive.

Similarly to the tests aimed at establishing the diagnosis of hypercortisolism, those directed at identifying the etiology of an ACTH-dependent Cushing’s syndrome, i.e. CD or ES, should be suitable for the detection of the low prevalence disorder which means, in our setting, highly sensitive for ES. Unfortunately, most of the tests nowadays available are geared towards the identification of CD rather than ES and this latter diagnosis is essentially established by the “failure to behave like CD”, e.g. absent response to CRH, absent gradient at inferior petrosal sinus sampling (IPSS). Given the gaussian distribution of most biological findings, a small percentage of “absent responses” (false negatives) in the disease with higher prevalence fatally compromises the diagnostic power of the test. In our series, the small number of patients with CD which failed to exhibit the expected diagnostic pattern at CRH stimulation or IPSS sampling was sufficient to markedly decrease the predictive value of a negative result (36% and 45%, respectively) although sensitivity of both tests was good (85%). In essence, we believe major efforts should be expended in order to find a test which will enable us to recognise the small number of patients with ES rather than confirm the strong a priori probability of CD.

Epidemiological data pertaining to the treatment of patients with CD are also of interest. In our cohort, a pi-

### Table I
Number of patients diagnosed per year.

<table>
<thead>
<tr>
<th></th>
<th>Cushing’s disease</th>
<th>Adrenal Adenoma</th>
<th>Adrenal Carcinoma</th>
<th>Ectopic secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>pts/year prior to 1987</td>
<td>7.4 ± 0.71</td>
<td>2.8 ± 0.89</td>
<td>0.7 ± 0.24</td>
<td>0.1 ± 0.11</td>
</tr>
<tr>
<td>pts/year after 1987</td>
<td>26.4 ± 4.12</td>
<td>6.7 ± 1.66</td>
<td>1.7 ± 0.64</td>
<td>2.9 ± 0.67</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± S.E.M.
pituitary adenoma was found and removed at transsphenoidal surgery in about 85% of patients. Removal of the adenoma was strongly linked to remission of the disease, indeed, remission was obtained in 75% of patients in whom the adenoma was removed during the surgical procedure compared to a remission rate of 36% if the adenoma was not found at surgery (table II). The adenoma was mostly localized in the lateral lobes, 47% in the right lobe and 35% in the left lobe with less than 20% situated midline. In our series, the location of the adenoma was correctly predicted by pituitary imaging or intersinus gradient at IPSS in 86% and 68% of patients, respectively, in agreement with other large studies [3, 4]. Pituitary imaging, however, was unable to predict remission after surgery as the successful removal of a pituitary adenoma was performed in equal proportion among patients with positive and negative imaging (table II). This finding reflects the large number of microadenomas which are undetected by pituitary CT/MR (approx. 40%) and the neurosurgeon is able to extirpate.

An issue crucial to the statistics of treatment outcome are the criteria employed to define the remission. These differ considerably in published studies, some authors requiring undetectable plasma cortisol levels, others a normalisation of UFC or normal cortisol suppression after low dose dexamethasone, others an absent response to CRH stimulation or insulin tolerance test [1, 2, 18, 27]. Apart from these biochemical parameters, clinical adrenal insufficiency requiring glucocorticoid replacement therapy should be present over a certain period of time. Further, it has to be emphasized that the biochemical parameters defining remission are not necessarily also predictive of relapse. In our series [13], the detection of normal or subnormal postsurgical UFC and cortisol levels carried little weight towards prediction of relapse (β = 0.63, N.S. and β = 0.99, N.S., respectively), whereas ACTH levels and cortisol peak values after CRH were positive covariates for this risk (β = 1.076, p < 0.05 and β = 1.096, p < 0.05, respectively). In addition, relapses were only recorded among patients responsive with both ACTH and cortisol to CRH stimulation after surgery. Other large-scale studies identified, at variance with our observations, other possible predictors of relapse, e.g. as short duration of glucocorticoid replacement therapy after pituitary surgery, younger age, visualization of the adenoma at pituitary imaging [2]. Relapses occurred, in our and other series, up to 10 years after surgery, thus other factors may emerge as useful predictors of relapse as our experience with surgically treated patients with CD increases. Available therapeutic options for patients in whom pituitary surgery was unsuccessful or followed by a relapse (repeat pituitary surgery, radiation therapy, and adrenalectomy) brought about a remission of hypercortisolism in nearly 80% of patients.

As regards the course of clinical manifestations of CD following successful pituitary surgery, it is well known that several signs (e.g. truncal obesity, hirsutism and bruisability) resolve after correction of hypercortisolism but others have been less well studied. In our series [13], overt hypertension resolved in 58% of patients and diabetes disappeared in 60% of patients. Other studies have reported marked improvement of muscle weakness, osteopenia and psychiatric disorders [6, 14, 15]. However, it has been our observation that some derangements of cardiovascular function appear to persist after successful surgery and a recent study reported an increased cardiovascular risk as late as 5 years after remission [7]. Physical well-being of patients also is not fully regained [23]. Overall, compared to the four-fold higher mortality reported by earlier series [9, 24], two recent studies demonstrated mortality rates comparable to those of the general population [23, 26] indicating that current management of CD-while still far from perfect- has definitively improved the outcome for these patients.

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