INVITED COMMENTARY

Pituitary tumors in the elderly

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The proportion of elderly subjects is growing in Western countries and, as a consequence, several diseases are now recognized with increasing frequency in the older segment of the population. Pituitary tumors are no exception to the rule. However, the presentation, diagnosis and management of pituitary tumors in the elderly, defined as patients older than 65 or 70 years depending on the different authors, have received little attention in the literature, probably because of the difficulty in collecting large series of elderly patients with adequate follow-up.

In this issue of *European Journal of Endocrinology*, Turner and coworkers (1) report on a series of consecutive patients aged over 65 years seen at an Endocrinology Department over the last 20 years. All types of pituitary lesion are included, but pituitary adenomas were by far the commonest. Since the study population was recruited from an Endocrinology Department, it is very likely that a referral bias played a role in the frequency of the different types of pituitary tumors, because patients with meningioma of the sellar region, suprasellar craniopharyngioma or intracavernous aneurysm of the carotid artery are usually referred directly to a Neurosurgical Department. Notwithstanding, the paper raises some interesting questions. Is the incidence of pituitary adenomas in the elderly rising? A population-based study reported a significant increase in incidence in 1970–1989 compared with 1950–1969, but subjects aged over 65 years showed an opposite trend (2). These data were interpreted as reflecting an improved endocrinological and neuroradiological diagnostic capacity that also led to an earlier discovery of pituitary tumors (2). In another epidemiological study performed in Japan and covering the period from 1989 to 1995 (3), the age-adjusted incidence of pituitary adenomas in people more than 70 years old was 2.36 per 100 000, not significantly different from that occurring in people less than 70 years old (1.91 per 100 000). However, there was a sex-related difference in elderly people, since men showed an increase and women a decrease in the age-adjusted incidence of pituitary adenomas. The data of Turner and coworkers, showing an increase in the number of elderly patients diagnosed in the period 1991–1995 in comparison with the period 1981–1985 (1), apparently seem to confirm the results of the Japanese study. If this trend is confirmed in future epidemiological studies, there are two likely explanations:

on the one hand the already mentioned rising proportion of elderly subjects, and on the other the higher incidence in elderly subjects of medical conditions, such as cerebrovascular disease or dementia, that are always more frequently investigated by neuroimaging techniques. If the latter proves correct, the percentage of the so-called 'pituitary incidentaloma' should increase specifically in this age group.

Is the frequency of the various subtypes of pituitary adenomas in the elderly different from that in the other age groups? The answer is probably yes, but there is a surprising absence of specific epidemiological data on this point. Even the study of Turner and coworkers fails to provide this information, although it could have been examined by comparing the percentage of the different adenoma types in the elderly with that observed in the rest of the patient population seen at the local Endocrine Clinic during the same period. The comparison with autopsy studies is not convincing. It is well known that the frequency of pituitary adenomas found in unselected autopsies is very high, approaching 25% in some series (4), in sharp contrast to the low incidence of clinically relevant tumors. It is, thus, highly debatable whether the pathogenesis of both conditions is similar. Notwithstanding, clinical series of pituitary adenomas in the elderly (1, 5, 6) reveal a higher frequency of nonfunctioning adenomas and a marked underrepresentation of hypersecreting tumors, especially prolactinomas. The latter is not surprising, since signs of prolactin hypersecretion in elderly subjects are not relevant and, usually, only large macroprolactinomas are diagnosed in this age group because of the symptoms of mass effect.

Despite several refinements in hormonal and neuro-radiological tools, there is still a delay of years between the onset of specific symptoms and the diagnosis of pituitary adenomas. Several factors contribute to make misdiagnosis of pituitary tumors more likely in elderly people. Hypogonadism is one of the earliest symptom in nonfunctioning adenomas, but its presence in post-menopausal women is clinically silent, whereas in the male it is often ascribed to misconception about the physiological decline of sexual function with increasing age. Other symptoms of pituitary hypofunction, such as those due to hypothyroidism and hypoadrenalism, may not be so apparent in the elderly; moreover, the interpretation of endocrine and biochemical tests may not be typical of that found in a younger population (7).

Visual defects secondary to compression of the optic pathway should lead to prompt diagnosis of a pituitary tumor in the young as in elderly patients, but the latter are often misdiagnosed as having other ocular diseases, such as cataract, macular degeneration and vascular retinal disease, which are particularly frequent in this age group. Concerning hypersecreting adenomas, delayed diagnosis of acromegaly and Cushing's disease in the elderly may occur because symptoms such as hypertension, glucose intolerance, asthenia, mood depression and arthralgias are rather prevalent, thus preventing adequate diagnostic work-up in elderly patients.

The last and, perhaps more important, still unresolved question is the treatment of pituitary adenomas in old subjects. Dopaminergic therapy should be used in patients with macroprolactinomas, whereas I feel that microprolactinomas, if incidentally discovered in an elderly subject, should not be treated at all, but simply followed up to ensure the lack of progression of the disease. Acromegaly in older patients seems to be milder than in younger patients and some authors have questioned whether specific treatments should be given at all in selected cases (8). However, considering the increasing life expectancy of the population, the availability of effective therapies, and the inferior quality of life of patients with active acromegaly, I deem it hardly justifiable to withhold treatment only on age grounds. Transsphenoidal surgery is usually considered the first choice therapy in acromegaly, leading to clinical and biochemical remission of the disease in about 60% of the patients and causing substantial symptomatic improvement in over 90% of cases (9). The cure rate in elderly subjects was excellent in the hands of an experienced neurosurgical team (10) and in the present series Turner and coworkers reported remission in all six operated elderly acromegalic patients. The excellent surgical results are probably explained by favorable prognostic characteristics (small tumor size, low mean growth hormone level) in this age group. On the other hand, medical treatment with somatostatin analogs has also been proposed as primary therapy because of its proven efficacy in elderly acromegalic patients (11). Because of the rarity of acromegaly in old age, I suppose it will be impossible to implement a trial testing which treatment is better. In the absence of irrefutable data, I think that the decision should be made on an individual basis, taking into account several aspects, such as availability of a skilled neurosurgical team, high costs of medical treatment, and general health and personal preference of the patient. Among the different treatment options, transsphenoidal surgery is clearly preferable in Cushing's disease because of its quick effect and high remission rate. Concerning the latter point, the study by Turner and coworkers, showing an unsuccessful surgical outcome in both of two operated patients with an adrenocorticotropin-secreting microadenoma, is at odds with the experience in several other centers. Even

though surgical series dealing specifically with elderly patients with Cushing's disease are lacking, no report ever suggested a negative influence of age at operation on surgical outcome, which is successful in 70–90% of patients (12). Nonfunctioning adenomas, the commonest pituitary tumor in the older age group, can be managed only by surgery, as medical treatment with dopaminergic drugs or somatostatin analogs is not effective, except in sporadic cases, in reducing tumor size. The only alternative is radiotherapy, but, in the usual setting of visual impairment due to compression of the optic pathway, the long time required for a beneficial effect is clearly disadvantageous. I believe that surgery should be performed whenever a patient presents with visual defect, unless surgical risks are unacceptably high, in which case palliative radiation therapy should be offered. As discussed by Turner and coworkers, much more debatable is whether surgery should be performed for incidentally discovered pituitary tumors in asymptomatic patients. Again, no data are available in the old age group of patients on which to base specific recommendations. In our department, the therapeutic advice for patients with an 'incidentaloma' is to remove surgically the lesion if it is larger than 1 cm. However, taking into account the usual slow-growing nature of incidentalomas, the anagraphic and, especially, the biological age of the patient are considered when deciding whether to operate on or simply follow up the pituitary lesion.

The report by Turner and coworkers is another step forward in gaining more precise knowledge relevant to the diagnosis and care of elderly patients with pituitary tumors.

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