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Cerebrovascular disease in patients with functional or non-functional pituitary adenomas.

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Abstract

Several studies have shown that patients with acromegaly have increased mortality rates for cardiovascular diseases and, cerebrovascular diseases (CVD). Similar associations have also been observed for patients with hypopituitarism or with non-functional pituitary adenomas. One aim of this review was to summarize these data. Another purpose was to discuss the relative importance of different risk factors for cardiovascular, and especially CVD, mortality among both patients with acromegaly, and patients with hypopituitarism or with and non-functional pituitary adenomas, or with hypopituitarism due to other causes.

Epidemiological data show consistent and high mortality rates in cardiovascular diseases (1.5 to 4-fold higher) and CVD (2 to 8-fold higher) among patients with acromegaly. Also patients with other pituitary tumors or hypopituitarism have enhanced risks for cardiovascular mortality (1.5 to 2-fold higher) and CVD deaths (2.5 to 3-fold higher). Especially patients with craniopharyngiomas seem to have extremely high risks for CVD. Moreover, female patients with pituitary adenomas or hypopituitarism seem to be at higher risk for CVD than male patients. The literature gives, however, no clear picture of whether treatment modalities or longstanding excess of GH secretion are most important as risk factors for the enhanced mortality in acromegaly. Correspondingly, experimental data and clinical studies clearly support the potential impact of cranial radiation therapy, surgical trauma and hormone insufficiencies, including growth hormone deficiency, as risk factors for CVD deaths among patients with pituitary adenomas and hypopituitarism, but the epidemiological studies have not been able to distinguish between the relative importances of these risk factors.

It is now well established that hypopituitary patients on conventional hormone treatment i.e. corticosteroids, thyroid hormones, and sex-steroid hormones, but unsubstituted growth hormone deficiency, have a shortened life expectancy due to cardiovascular mortality. The majority of the patients with hypopituitarism have a history of operated and irradiated pituitary adenoma. The risk excess was greater in females than in males. A high cerebrovascular mortality was particularly prominent, whereas the enhanced risk for cardiac diseases was less impressive. Also, with regard to for cerebrovascular mortality, women were more affected than men. Excluded from these analyses were patients with acromegaly and Cushing's disease, as were patients with substituted growth hormone deficiency. This review will deal discuss with the recent research in this field and discuss the possible causes of the increase in cerebrovascular mortality in patients with hypopituitarism. Further, this review will focus on epidemiological studies in this are.

Teaser: Causes of the increase in cerebrovascular disease in patients with pituitary adenomas.

1. Introduction (controversial issue, try to summarize key studies and different hypothesis).
2. Epidemiological studies of cerebrovascular disease in patients with hypopituitarism. (the five studies, focusing on CVD).
3. Hypothesis of causal factors for increased CVD among hypopituitary patients.
 - 3.1. Cranial radiotherapy (CRT) and CVD.

Mechanistic aspects (arterial).
 - 3.1.2. Epidemiological studies of CRT and CVD.

Surgical trauma and CVD.
 - 3.3. Hormonal dysfunction and CVD
 - 3.3.1. GH deficiency and GH hypersecretion.
 - 3.3.2. Other hormonal dysfunction (estrogen and steroids).
4. Gender difference in CVD.
5. Conclusion. (Balanced).

1. Introduction

There have been limited attempts to estimate the occurrence of hypopituitarism and nonfunctional pituitary adenomas in the general population. A Spanish study came up with an incidence estimate of approximately 40 new cases of hypopituitarism per million person years, and prevalence figures of about 0.3-0.5 ‰ [1]. A major cause of hypopituitarism is pituitary adenomas. Information on the true prevalence and incidence of pituitary adenomas are scarce. In 1992 The the annual age- and sex-standardized incidence of clinically diagnosed pituitary adenomas (excluding acromegaly and Cushing's disease) in Sweden was 11 cases/ per million inhabitants person-years in 1992 [2]. (1). The mean age at diagnosis of these tumours was 52 years [(2,12,31,2)]. However, non-symptomatic pituitary adenomas seem to be very prevalent in the general population. Postmortem and imaging studies have shown prevalence estimates ranging between <1 % to >30 %, with an overall estimated prevalence of about 17 % ([4]Ezzat et al 2004). Pituitary adenomas can be secreting or nonfunctioning non-functioning and these clinically diagnosed tumours are effectively treated with a combination of surgery, cranial radiotherapy (CRT) and medical therapy. Radiotherapy CRT may be employed as a treatment modality to reduce the regrowth rate of incompletely resected nonfunctioning non-functioning adenomas and in secreting pituitary tumours tumors where hormonal control cannot be achieved with surgery and medical therapy [(3-55,6,7)]. Without radiotherapy CRT the recurrence rate of nonfunctioning pituitary adenomas is was 68.53 % at 10 years and 47.67 % at 15 years after operation [(68)]. In comparison, With radiotherapy CRT combined with limited surgery, resulted in a regrowth of 7 % to and 12 % of the nonfunctioning pituitary adenomas have had a regrowth within 10 and 15 years, respectively [(8,96,7)].

The conventional treatment for

Patients with hypopituitarism are treated conventionally, which includes substitution with corticosteroids, thyroid hormones, and sex-steroid hormones. Only recently growth hormone (GH) has been a suggested treatment when there is a confirmed GH deficiency (GHD) of this hormone [810]. Most patients with pituitary adenomas have experienced unsubstituted hypopituitarism. The most common reason for hypopituitarism is also pituitary adenomas. Thus, there is a considerable overlap between these concepts. Some studies have been performed on patients with pituitary adenomas, while other studies were based on defined cases of hypopituitarism. This may cause some confusion, but we have tried our best to present the study bases as clearly as possible in this review.

Functioning pituitary adenoma causing acromegaly have to be considered in parallel with those of other pituitary tumors. The average incidence of acromegaly has in different studies been estimated to about 3-4 cases per million person-years, and the prevalence to between 0.04 and 0.07 % [(Alexander et al 1980, Bengtson et al 1988, Ritchie, Etxabe et al 199311-14)]. There are indications of increasing incidence over later calendar-year periods, indicating previous under diagnosis [(Etxabe et al 199314)].

It is not a controversial issue that patients with acromegaly have increased risks for *cardiovascular diseases* (ICD 8th revision; 390-429, 430-438, 440-459), and more specifically for the subgroup of *cerebrovascular diseases* (CVD) (ICD 8th revision; 430-438). However, what might be debatable is rather which disease determinants or treatment modalities that are associated with the risk excesses. A slightly more controversial issue has been whether also patients with other types of pituitary tumors than those causing acromegaly, and patients with hypopituitarism, have been subjected to increased cardiovascular and CVD mortality. These concerns have been based on epidemiological studies [(REF3, 15,16)], but also clinical studies of risk factor profiles have supported these suspicions [(REF17,18)]. One aim of this review was to summarize available data on cardiovascular and CVD mortality risks for

patients with acromegaly as well as for patients with non-functional adenomas and hypopituitarism.

Another, and more challenging aspect of this review is to discuss the relative importance of different risk factors for cardiovascular mortality, and especially for CVD mortality, in these different groups of patients. With respect to acromegaly the task is to try to distinguish between effects of pre- and post-treatment periods of excess GH secretion and effects of the treatment modalities (mainly CRT and surgery). The risk factors for patients with non-functioning pituitary tumors or hypopituitarism comprise CRT, surgical trauma to the vasculature, and pituitary hormone insufficiencies, including GHD, enhancing atherosclerotic processes. There is no obvious consensus about which disease determinants or treatment modalities that acts as risk factors for these diseases, or how relatively important they are. Tentative schemes of causal-chains of events leading to CVD mortality in acromegaly and in patients with non-functioning pituitary tumors or hypopituitarism are outlined in Figures 1 and 2.

We want to emphasize that it is a difficult task in longitudinal epidemiological studies to clarify the relative impact on cardiovascular and CVD mortality of different disease determinants and treatment modalities. Few studies have been large enough, and with appropriate distribution of the potential risk factors, to allow a conclusive evaluation of their relative impact. A prerequisite for a balanced assessment is therefore to take into account not only mortality data but also consider the biological plausibility based on circumstantial evidence from experimental and clinical studies.

Finally, we have to stress that different traditions of disease terminology may cause some confusion. We, as many others, prefer to define CVD as a subgroup of cardiovascular diseases, but there are a number of researchers that has considered CVD as a diagnostic entity not included in the concept of cardiovascular disease. In some studies the disease

classification is explicit, but in others there remain an unfortunate lack of clarity with respect to this.

It is now has been shown well established that hypopituitary patients on conventional hormone treatment, but unsubstituted growth hormone deficiency, have a shortened life expectancy due to cardiovascular mortality (Rosen, Bulow, Tomlinson) and particularly cerebrovascular mortality (Bulow, Tomlinson). A high cerebrovascular mortality was particularly indicated prominent, and women were more affected than men (Bulow, Tomlinson). These findings are based on large cohort studies from both Sweden and the UK. Even if the conventional hormone treatment has differed somewhat between among studies (e.g. different corticosteroids have been used, with cortisone acetate in the Swedish studies and hydrocortisone in the UK studies), the cardiovascular mortality was almost the same.

The cause of the increased cardiovascular mortality in patients with hypopituitarism, is however, not known clarified. Premature atherosclerosis caused by GH deficiency, or from preoperative long-standing unsubstituted or postoperatively inadequately substituted insufficiencies of other pituitary hormones has been suggested. The impact of radiotherapy has been discussed .. Utveckla.

The impact of GH deficiency for the increased cardiovascular mortality has been discussed and there are numerous reports showing an increment of cardiovascular Today there are numerous reports on the Medline (March 2004, 916 reports), reporting an increase in cardiovascular risk factors in patients with hypopituitarism on conventional hormone treatment, and unsubstituted GH deficiency. These risk factors, including lipid abnormalities, increase in fat mass and reduction in lean mass, high waist/ hip ratio, insulin resistance, and

vascular endothelial dysfunction (9,10). In a recent meta-analysis based on thirty-seven clinical trials, GH treatment has been had beneficial effect on lean and fat body mass, total and LDL cholesterol, and diastolic blood pressure, but reduced insulin sensitivity (Maison et al 2004) shown to reverse many, but not all, of these risk factors (9,10). .

In patients with acromegaly there is particularly an increased risk of cerebrovascular disease (Orme). In a recent report patients with acromegaly subjected to CRT had an increased CVD mortality. It was suggested that CRT may be the contributing cause for CVD. However, no information on non-CRT patients was provided. Further, there seem to be convincing evidence, based on cardiovascular risk factors, for the increase in cerebrovascular disease in patients with acromegaly, with e. g. hypertension, insulin resistance and diabetes mellitus, cardiac rhythms disturbances, and lipid derangements (review Colao).

2. Risks for CVD mortality Epidemiological studies of cerebrovascular disease in among patients with y of cardiovascular disease in patients with hypopituitarism and pituitary adenomas

2.1. Acromegaly

Among 194 patients with acromegaly 13 cases of cardiovascular deaths had occurred corresponding to a Standardized Mortality Ratio (SMR) of 1.57 (95 % Confidence Interval [CI] 0.83-2.68) [(Wright et al 1969 19)]. Moreover, another 8 cases of CVD deaths had occurred, corresponding to an SMR of 2.86 (95 % CI 1.23-5.63).

In a retrospective cohort of 164 pt with acromegaly 13 cases of cardiovascular deaths (ICD codes 393-429) had occurred, corresponding to an SMR of 2.89 (95% CI 1.54-4.94).

[(Alexander 198011)]. Moreover, another 14 cases of CVD deaths had occurred, corresponding to an SMR of 8.24 (95% CI 4.50-13.8).

Among 166 pt with acromegaly long-term follow up showed a significant 3.5-fold increased cardiovascular mortality [(Bengtsson et al 198812)]. Eleven of the 32 deaths in cardiovascular diseases died from CVD, but no comparison data for CVD were presented.

In a small consecutive series of 74 patients, 10 deaths occurred, corresponding to an SMR of 3.22 (95% CI 1.55-5.93; [Etxabe et al 199314]). The authors claim an enhanced SMR of 10 for cardiovascular disease among men, but this was based on only one incident case (95 % CI 0.25-56) and does therefore not provide much of evidence. CVD mortality was not evaluated in this study.

In an UK cohort study of 1362 patients with acromegaly, mortality rates due to cardiovascular diseases (SMR 1.76, 95 % CI 1.47-2.07) and CVD (SMR 2.06, 95 % CI 1.50-2.76) were increased [(Orme et al 199820)]. The most striking finding was the high CVD mortality occurring in acromegalic patients diagnosed under 35 yr of age (SMR 7.36; 95 % CI 3.18 –14.5). There was a significant trend that higher post-treatment GH-levels (> 2.5 µg/l) predicted increased overall and cardiovascular mortality. However, with respect to CVD mortality no such trend could be established in a significant way.

In a recent study, an SMR of 2.68 (95 % CI 1.73-4.15) for CVD mortality was observed in a cohort of 419 patients with acromegaly [(Ayuk et al21)]. A GH reduction after treatment to 2 µg/l indicated a better overall survival (p=0.07). No evaluation of the impact of GH reduction on CVD mortality was performed.

In a study of 208 consecutive patients from New Zealand with acromegaly, overall and cardiovascular mortality was increased as compared to the general population during a 30 year follow up period (Holdaway 2004). The cardiovascular mortality rates seemed to be reduced to the expected community levels by achieving GH concentrations less than 1-2 µg/l.

No specific evaluation of CVD mortality was performed. To sum up, there is a good coherence in published epidemiological studies indicating that patients with acromegaly have suffered a 1.5 to 4-fold risk excess for cardiovascular mortality and a 2 to 8-fold risk excess for CVD mortality.

2.2. Other pituitary adenomas and hypopituitarism

(Tables 1 and 2).

Totally five cohort mortality studies have been performed so far (REF; Table 1). The A first Swedish cohort study comprised 333 patients with hypopituitarism, in 77 % of the cases due to treatment of a pituitary tumour [(1115)]. The The results showed a significant increase doubled in cardiovascular mortality (Relative Risk [RR] 1.95Table 21). No analyses with respect to CVD mortality were performed.

The risk excess was greater in women than in men. In the a first study from the UK [(1222)] comprising the inclusion criterion of hypopituitarism was met for 172 patients with hypopituitarism, and the diagnosis was in 76 % due to treatment of a pituitary tumour. A slight and but statistically non-significant increased cardiovascular mortality was observed (Standardized Mortality Ratio [SMR] 1.35). No analyses with respect to CVD mortality were performed.

TheA second Swedish cohort study comprised 344 patients with hypopituitarism, in all cases due to treatment of a pituitary tumour [((pituitary adenomas (in 88 %) and craniopharyngiomas (in 12 %;)) ([3]2). The results showed a significant 75 % increase in cardiovascular mortality. Of special interest was the more than three times increased (SMR 1.75) and particularly . The risk excess was greater in females (SMR 2.39) than in males

(SMR 1.54). Considering specific vascular diagnoses, the greatest risk excess was seen for cerebrovascular CVD mortality (SMR 3.39, 95 % CI 2.27-4.99), while whereas the enhanced risk for cardiac diseases was less impressive (SMR 1.41).

Also for cerebrovascular mortality females had been at a greater risk (SMR 4.91) than males (SMR 2.64) (Fig 1).

In the TheA second mortality study from the UK [(1323)] comprised 335 patients and the inclusion criterion was surgery for a pituitary tumour and not hypopituitarism. The cardiovascular mortality was non-significantly reduced, however, only among the females (SMR 0.5), but no analyses with respect to CVD mortality were presented.

Finally, in the latest mortality study from the UK, including included 1014 patients with hypopituitarism, of whom 573 (57 %) were had nonfunctioningnon-functioning adenomas, 118 (12 %) craniopharyngiomas, and the rest other causes of hypopituitarism e.g. prolactinomas, idiopathic hypopituitarism, empty sella syndrome, gonadotropinoma, Sheehans syndrome and thyreotropin-secreting tumours [(1416)]. A significant almost doubled cardiovascular mortality was observed. The risk excess was even more prominent for The excess mortality was due to cardiovascular mortality diseases SMR 1.82 (95% Confidence Interval (CI) 1.62-2.16) and particularly cerebrovascular CVD mortality (SMR SMR 2.44, (95 % CI 1.58-4.18).

Univariate analyses indicated that mortality was higher in women (SMR 2.29, 95% CI 1.86-2.82), younger patients, patients with an underlying craniopharyngioma (SMR 9.28, 95% CI 5.84-14.75), and in patients (n=353) treated with radiotherapy (SMR 2.32, 95% CI 1.71-3.14).

In the group of patients with nonfunctioning pituitary adenomas (n=573) as the underlying cause of hypopituitarism, excess mortality was explained by an increase in respiratory and cardiovascular deaths. and was also increased in women compared to men. Univariate analyses revealed however, no effect on of surgery or radiotherapy in this sub-cohort. In a A multivariate analyses of the entire cohort (n=1014) included the following variables; age, sex, diagnosis of craniopharyngioma, all hormone deficiencies, radiotherapy, and surgery. Only a diagnosis of craniopharyngioma, younger age at diagnosis, **and untreated gonadotropin deficiency** turned out as independent factors affecting mortality, and not radiotherapy or surgery.

In all these five cohort studies, patients with acromegaly or Cushing's disease were excluded and no patients with GH replacement were included. Further, in all studies with the inclusion criterion of hypopituitarism, this was defined as documented clinical and/or biochemical deficiency in at least one endocrine axis. Moreover, all deaths within one month postoperatively were excluded.

Two other studies with somewhat different study design are also worth mentioning. In an UK cohort of the incidence of CVD accidents was assessed. A drawback was, however, that also 41 patients with acromegaly and 10 patients with Cushing's disease were included in the patient material of 331 patients with pituitary adenoma [(2024)]. A fourfold increase of CVD accidents registered in medical records was observed, as compared with expected figures derived from the general population.

In a Swedish register-linkage study, 1411 adult patients that had obtained inpatient care 1987-1992 with a primary or secondary diagnosis of hypopituitary disease (excluding acromegaly or Cushing's disease) were identified and followed from time of care to next time of inpatient care up to 1994, or to time of death [(Svensson et al 2004)25]. No information on

disease characteristics, hormone deficiencies or treatments was available. Expected morbidity data derived from the general population was obtained from the Swedish Hospital Discharge Register, and expected mortality was obtained through the Swedish Cause-of-Death Register. The risk ratio (RR) for cerebrovascular events was 2.74 (95 % CI 2.21-3.35), while less impressive for myocardial infarctions (RR 1.40, 95 % CI 1.10-1.75).

2.3. Craniopharyngiomas

Craniopharyngioma is not a pituitary adenoma, but this tumor is an important contributing factor to hypopituitarism [26,27]. Craniopharyngioma is not a pituitary adenoma, but this tumor is an important contributing factor to hypopituitarism. Craniopharyngiomas account for approximately 1.2-4% of all intracranial tumours [28]. The treatment of these tumours is surgery and to reduce recurrence radiotherapy is often employed. A study from the US based on population-based tumour incidence registries comprising also craniopharyngiomas, showed an overall incidence of 0.1 per 100 000 person-years [29]. Separate analyses for this subgroup of patients have been made for some of the cohorts. In a Swedish cohort of 60 patients with craniopharyngiomas the cardiovascular mortality was enhanced (SMR 3.21, 95 % CI 1.29-6.61), but no specific analysis was made for CVD deaths, due to the small cohort size [(Bülow et al 1998).27]. In an UK cohort, an extremely high SMR of 19.4 (95 % CI 8.08-46.7) for CVD, was observed for the subgroup of 118 patients with craniopharyngiomas [(1416)].

2.4. Gender aspects

Stratifying the results of a small cohort study comprising 94 patients with acromegaly for gender indicated that the risk excess for cardiovascular mortality was higher among men (SMR 2.01, 95 % CI 0.92-3.81) than among women (SMR 1.04, 95 % CI 0.28-2.65), but no

such gender-difference was seen for CVD mortality [(Wright et al 1969)19]. A similar pattern was seen in another cohort and based on few observations; SMR for cardiovascular mortality was 4.21 (95 % CI 1.82-8.30) for men and 1.92 (95 % CI 0.62-4.50) for women [(Alexander et al)11].

In the first Swedish cohort study of patients with hypopituitarism, a nominally but not significantly higher risk for women than for men was seen for cardiovascular deaths [(Rosen & Bengtsson15)]. No analyses were performed for CVD. An increased cardiovascular risk for women as compared to men was also seen in the second Swedish cohort study, but the risk difference was more impressive for cerebrovascular disease (SMR 4.91 vs. 2.64) (Figure 3) [3]. In the UK study of CVD accidents, there was a significantly higher risk for women than men with pituitary adenoma, when comparisons were made with the general population (Relative Risk 6.1 vs. 2.9) [(2024)]. Finally, the same pattern was observed in a Swedish register-linkage study showing higher RR for cerebrovascular events among women (3.46, 95 % CI 2.53-4.61), than among men (RR 2.27, 95 % CI 1.71-3.02) [25].

It is possible that the gender difference for cardiovascular and CVD events might be due to that women with hypopituitarism have experienced an unfortunate exposure to sex-hormones over their life-span. The patients have experienced a longer or shorter period before diagnosis of unsubstituted hypogonadism combined with post-diagnostic hormone replacement therapy for estrogens and gestagens. Recent results from the clinical trial Women's Health Initiative have clearly shown significantly increased risks for both CVD and coronary heart disease among women belonging to the arm given estrogens and gestagens and increased risk for CVD, but not for coronary heart disease, among women belonging to the arm given estrogens only [(Barret-Conner 2003, Anderson et al, JAMA 2004)30,31]. Thus, both the period of hypogonadism relatively early in life and the often long-term

unphysiological substitutions with estrogens and gestagens may explain why female patients seems to have been at higher risk than male patients.

2.5. Conclusions

The epidemiological studies support an increased cardiovascular mortality, not only in patients with acromegaly, but also in patients with pituitary adenomas and other causes of hypopituitarism. Moreover, in studies where specific analyses have been performed, the results supports that the patients are especially at risk for CVD. Available data also indicate that especially patients with craniopharyngiomas have extremely high risks for CVD. Finally, female patients with pituitary adenomas and hypopituitarism seem to be at higher risk for CVD than male patients, while limited data support that men with acromegaly are at higher risk for cardiovascular deaths than women.

3. Potential risk factors for increased CVD among patients with acromegaly

A problem interpreting risk the relative impact of different risk factors in some of the previous mortality studies of patients with acromegaly is that information on CRT was missing [(Orme 1998, Alexander 1980)20, 11]. In the study from Bates et al [(1993)32] and Bengtsson et al [(1988)12] the majority (63 % and 53%, respectively) were irradiated but in the study by Wright et al [(1970)19], only 19 % of the patients were irradiated.

Unfortunately, no evaluation of the impact of CRT on mortality was provided in any of these studies.

In a study of 162 patients with acromegaly that underwent transsphenoidal surgery, those 86 considered cured at operation had no increased overall SMR as compared with the general US population, but those with persistent active disease measured by not normalized

GH levels in serum had an SMR of 1.8 (95 % CI 0.9-3.6) [(Swearingen et al 1998)33]. No analyses with respect to cardiovascular or CVD mortality were performed.

There was in a large UK cohort study of more than 1300 patients a significant trend that higher post-treatment GH-levels ($> 2.5 \mu\text{g/l}$) predicted increased overall and cardiovascular mortality [20]. However, with respect to CVD mortality no such trend could be established in a significant way.

A follow up of a series of 254 consecutive patients with acromegaly that had undergone transsphenoidal surgery showed a three-fold overall enhanced mortality among those with persistent disease as compared with no excess mortality for those in remission, as defined by normalised GH levels [(Abosch et al 1998)34]. In this material only 13 patients had obtained CRT. No analyses with respect to cardiovascular or CVD mortality were performed.

Among 208 patients with acromegaly in a cohort from New Zealand almost all had received some surgical treatment and 181 of them had also obtained CRT [(Holdaway et al 2004)35]. Unfortunately no reliable comparisons were made with expected mortality based on the general population, but internal analyses showed that overall survival was in a multivariate model dependent on age, serum GH levels, duration of symptoms before diagnosis, and hypertension. GH concentrations less than $1\text{-}2 \mu\text{g/l}$ did not seem to be associated with increased cardiovascular mortality. No analyses with respect to CVD mortality were performed.

In a small follow up study of 103 patients with acromegaly from Canada that had underwent transsphenoidal surgery the follow-up showed a significant five-fold excess (based on 13 incident deaths) in overall mortality as compared with the general population for patients with persistent disease as measured by high GH levels in serum, but no excess for patients in remission [(Beauregard et al 2003)36]. No analyses with respect to cardiovascular or CVD mortality was performed.

In a recent study by Ayuk et al, [21] an SMR of 4.42 (95 % CI 2.71-7.22) for CVD mortality was observed among a mixed group of 91 patients with acromegaly with CRT only (40-50 Gy) and 120 with both surgery and CRT (REF). This was in contrast to the total lack of increased CVD mortality among the remaining cohort of 136 patients with surgery alone and 71 with somatostatin treatment (SMR 1.0). Unfortunately, no adjustment for potential confounding factors was made when analysing for CVD mortality. The presence or absence of hypopituitarism was said not to have affected the mortality risk, but it seems unclear what proportion of the cohort that had been subjected to such an evaluation. A GH reduction after treatment to 2 µg/l indicated a better overall survival (p=0.07). No evaluation of the impact of GH reduction on CVD mortality was performed.

Available data support that low post treatment GH-levels seem to counteract the excess risk for cardiovascular mortality, but the impact on CVD mortality has not been studied. What may speak for that longstanding excess GH secretion before diagnosis contributes to a subsequently enhanced mortality risk for CVD, is an observed significant positive relation between duration of acromegaly and CVD mortality [(Orme et al 1998)20]. Hypertension is very common in acromegaly and reported in 30-40 % of the patients [(Nabarro 1987, review Colao37)]. Also other cardiovascular risk factors, such as e. g. insulin resistance and diabetes mellitus, cardiac rhythm disturbances, dilated cardiomyopathy, valvular heart diseases, and lipid derangements, are more common among patients with acromegaly than in the general population [(37)Colao 2003, **Kahaly 1992, Rodrigues 1989, 21, 137**]. It is also possible that structural changes in the vascular system, caused by e.g. hypertension [(ref 35 i38] **Orme 1998**), are not ameliorated by lowering GH levels.

34. Hypotheses of Potential causal risk factors for increased CVD among patients with other pituitary adenomas and hypopituitarism

It is not an uncomplicated task trying to assess the relative impact of different risk factors for the excess of cardiovascular and CVD mortality among patients with hypopituitarism and pituitary adenomas other than those secreting GH. A reason for this is the complicated interaction between the risk factors, which is illustrated in Figure 2. It is not possible even by multivariate analysis to separate the effect of different factors if they are involved in the same causal chain of event. Moreover, the uneven distribution of some risk factors in the study bases, and the lack of information for some of these risk factors in some studies, makes this task even more difficult.

In order to investigate if the types of CVD are the same among patients with hypopituitarism and due to pituitary adenomas as in the general population, deceased CVD cases from the cohort were compared with randomly selected control patients from the general Swedish population, who also had died from CVD and were matched for age, calendar year of death, gender, and hospital code [(2139)]. There were, however, no significant differences between the groups with respect to the infarction/hemorrhage ratio, type of clinical stroke syndrome and time to death after stroke. It should be borne in mind that the relatively few available cases of CVD deaths in the cohort limited the statistical power to exclude more than relatively large differences.

hypopituitary patients.

34.1. Cranial radiotherapy (CRT) and CVD and CVD

Hypopituitarism and cerebrovascular disease (CVD)

Hypopituitarism is a well-documented consequence of irradiation of pituitary adenomas or other brain tumors (15,16). Information on hypopituitarism has however, been missing in the

majority of previous studies reporting stroke after radiotherapy for cerebral tumors (17-20). A novel observation in the recent study from Erfurth et al (21) was that among the female patients who died of CVD, and also had the highest SMR's for CVD deaths (2), a significantly longer duration of symptoms for hypopituitarism before operation was recorded. No such difference was seen among the males. Thus, it is possible that unsubstituted pituitary insufficiencies before operation, e.g. gonadal insufficiencies, contributed to this increased mortality. This is in accordance with a recent finding that untreated gonadotropin deficiency was shown to be an independent significant factor affecting mortality in patients with hypopituitarism (14).

The incidence of non-fatal vascular disease has hitherto only been assessed in females with hypopituitarism and unsubstituted GH deficiency (22). Compared to controls recruited from the general population, and matched for sex, age, smoking habits, educational level, and residence, an increased relative risk (RR) for cardiovascular incidence (3.7; 95% CI 1.2-11.3) was found, including both cardiac and cerebrovascular diseases. Furthermore, the consumption of cardio-active drugs was also significantly higher in patients than in controls.

34.1.1. Mechanistic aspects **Arterial response to radiation**

Effects of radiation on cerebral vasculature

Vascular complications occasionally follow irradiation of pituitary tumors (17-20). The most dramatic reports are of children who suffered stroke after irradiation and had clear arteriographic changes within the radiation fields (23). Bowen and Paulsen (17) presented two cases of cerebral infarction, 13 and 20 years after cranial irradiation for pituitary tumours, and suggested that pituitary radiation increases the risk of a subsequent stroke.

Human and animal studies have shown that therapeutic radiation CRT can induce arterial injury and lead to an atherosclerosis-like occlusive disease [(2440)]. Of the cerebral vasculature, capillaries and endothelial cells seem to be the most radiosensitive [(2541)]. Radiation CRT-induced changes in the cerebral arterial wall are determined by a number of cellular processes in endothelial and smooth muscle cells that modulate differences in radiosensitivity radio sensitivity and phenotypic expression [(2541)]. The histopathological findings in arterial radiation injury include vessel wall thickening, thrombosis, luminal occlusion, and occasional telangiectases. Further, characteristic changes in capillary histology include detachment of endothelial cells from the basal lamina, cell pyknosis, thrombosis, and loss of entire capillary segments, resulting in tissue ischemia or regrowth of lost vessels in some organs [(2642)]. This capillary injury may be the crux of tissue radiosensitivity. Endothelial cells exhibit however, significant repair capacity and recovery potential after radiation insult [(2743)]. The median and large arteries are mainly affected through injury to vasa vasorum.

34.1.2. Clinical and Eepidemiological studies of CRT and CVD.

Vascular complications occasionally follow CRT of pituitary tumors [(17-2044,45,46,24)]. The most dramatic reports are of children who suffered stroke after irradiation and had clear arteriographic changes within the radiation fields [(47)23). Bowen and Paulsen [(1744)] presented two cases of cerebral infarction, 13 and 20 years after CRT for pituitary tumours, and suggested that pituitary radiation increases the risk of a subsequent stroke.

Conventional radiotherapy as a cause of CVD in patients with pituitary adenomas

Numerous case reports implicate radiotherapy of the brain in the development of cerebrovascular injury (24). Bowen & Paulsen (17) presented two cases of cerebral infarction,

13 and 20 years after cranial irradiation for pituitary tumours, and suggested that pituitary radiation increases the risk of a subsequent stroke. Hashimoto et al [(1946)] investigated 139 patients with a pituitary adenomas that who received a radiation dose of 40-60 Gy. Ten patients suffered cerebral ischemic events, three of which were considered to be caused by radiation angiopathy because of their atypical occlusive patterns. Strokes occurred 5, 7 and 8 years after irradiation. These early studies were mostly descriptive and lacked both appropriate comparison groups and detailed dosimetry.

Flickinger et al [(1845)] recorded 7 cases of cerebral infarction among 156 patients treated with CRT for a pituitary adenoma. The CVD cases had in multivariate analyses not higher biological equivalent dose (BED) of irradiation, which more accurately reflects the neural tissue tolerance, than other patients. A caveat with this interpretation was the low statistical power in this small study.

The studies mentioned have been mostly descriptive and no appropriate groups for comparison have been provided. In a recent study from the UK, CVD mortality was assessed in a cohort of 334 patients with either nonfunctioning or secreting pituitary adenomas (including acromegaly and Cushing's disease) treated with surgery and post operatively with 40-50 Gy CRT [(2048)]. A significant four-fold risk for CVD deaths was recorded, as compared to the general population. Brada et al (20) reported a four-fold risk for CVD accidents in patients irradiated for a pituitary adenoma compared to the general population. The risk was higher in women than in men. TheA weakness with the study design was that the conclusions from this study can, however, be questioned because the expected incidence used for comparison was calculated from a different calendar-year period, and than the one for the cohort. the interpretation was also complicated because Moreover, patientspatients with acromegaly were included in the cohort together with patients with nonfunctioning adenomas.

Finally, a drawback with this study was that no detailed dosimetry or dose per fraction was provided.

In another UK cohort, there was in univariate analyses an increased risk for CVD among pituitary adenoma patients that had underwent CRT as compared with the other patients with pituitary adenoma, but in a multivariate analysis taking also age, gender, diagnosis of craniopharyngiomas, hormonal deficiencies, and surgery into account, this association disappeared [(1416)]. However, *and these patients have an increased CVD mortality (28)*. In contrast to the results from Brada et al (20), Tomlinson et al (14) reported that radiotherapy was not a factor determining mortality outcome in a sub-cohort of patients with hypopituitarism due to a nonfunctioning pituitary adenoma. no CRT dosimetry data were provided.

There are previous stroke incidence studies on in patients with pituitary adenomas (18-20,29), but, except for the study by Flickinger et al (18), a detailed dosimetry of radiotherapy has not been given in these studies. In the study from Brada et al (20) no detailed dosimetry or dose per fraction was provided, thus,

a reliable and comparable assessment was difficult. The first detailed study of stroke CVD deaths risks in patients with operated and irradiated pituitary tumours, providing both a detailed dosimetry and comparisons with population controls, was from Erfurth et al [(2139)]. A more than threefold increase in CVD deaths compared to expected values derived from the general population, was observed [(213)]. An internal comparison in the cohort between In a cohort of 342 patients operated and irradiated for pituitary tumors, 31 patients died from CVD (CVD patients) between 1952 and 1996. The majority of the patients were diagnosed with chromophobic chromophobic adenomas (n=288), craniopharyngiomas (n=26), and the remaining were prolactinomas and gonadotropinomas (21). The 31 CVD patients were

compared with 62 control matched patients from the same cohort that who had not died from CVD, but were matched for (control patients). The matching was made for gender, age at radiation, and time of follow up. , showed No significant differences in maximum or centrally absorbed dose, maximum or central biological equivalent dose (BED), field size, or number of fraction, were recorded between CVD and control patients (Table 32). However, in similarity with the study by These results are consistent with Flickinger et al [(1845)], the statistical power allowed only exclusion of relatively strong associations. who studied 156 patients after irradiation for a pituitary adenoma and recorded an increased incidence of cerebral infarction (observed 7 cases vs expected 3.5). In accordance with the previous study (21), the equivalent dose, that which more accurately reflects the neural tissue tolerance, was calculated and in a multivariate analyses the increased incidence of stroke was associated with age, but not with equivalent dose of irradiation. It has to be pointed out however, that the range of CRT was

In a recent study from the UK, CVD mortality was assessed (30) in a cohort of 334 patients known to have increased incidence of CVD accidents (20). The vast majority of the pituitary tumours were nonfunctioning and secreting pituitary adenomas (including acromegaly and Cushing's disease) treated with surgery and post operative radiotherapy. The patients received postoperative radiotherapy to a usual dose of 40-50 Gy in 20-30 fractions, using with the use of conventional three-fields techniques. An increased risk for CVD mortality compared to the general population with a relative risk (RR) of 4.11, 95% CI 2.84-5.75, which mirrored the increased incidence of CVD accidents, was recorded. Further, the CVD mortality was significantly higher in women (RR 6.93, 95% CI 4.29-10.60), compared to than in men (RR 2.4, 95% CI 1.24-4.20; $p = 0.002$). Three deaths were from subarachnoid haemorrhage compared to 0.54 expected (RR 5.51, 95% CI 1.14-16.09) was recorded.

Furthermore, the relative risk in patients with nonfunctioning tumours was 3.65 (95% CI; 2.26-5.58), compared with 5.23 (95% CI 2.25-10.30) in secretory tumours and was not significantly different ($p=0.4$). A more detailed analysis of the aetiology of the CVD accidents or deaths, was however, was not performed.

Radiosurgery in patients with pituitary adenomas

To date there is no information of long-term disease, hormonal control, ofon incidence or mortality of CVD, in patients with pituitary adenomas treated with stereotactic radiosurgery (SRT) or fractionated stereotactic radiotherapy (SCRT) [(3149)].

To sum up, experimental data and case reports clearly support that CRT may act as a risk factor for CVD, but available epidemiological studies do not provide any clear evidence pinpointing CRT as a stronger risk factor than other risk factors discussed in this review. Unfortunately, only two studies provided sufficient dosimetry information [(39, 45)18, 21), and none of them supported any dose-response association with CVD. After short term follow up, there was no tendency, however, of lower risk of developing hypopituitarism after SRT or SCRT compared to conventional external beam radiotherapy (31,32).

Evaluation of stroke in patients with pituitary adenomas

In a recent study (21) on patients operated and radiated for pituitary tumours an attempt to further elucidate the background mechanisms of stroke, the infarction/hemorrhage ratio, type of clinical stroke syndrome and time to death after stroke was made. This cohort included 342 patients operated and irradiated for pituitary

tumors between 1952 and 1996, and 31 patients had died from CVD (CVD patients). Potential control patients that had died from CVD, matched for age, calendar year of death, gender, and hospital code, were randomly selected from the general population (population controls), using the cause-of-death register. The Oxfordshire Community Stroke Project (OCSP) classification was used to classify them into four different *clinical stroke syndromes* (33). The *type of stroke* (infarction or hemorrhage) was based on computerized tomography (CT), angiography, or autopsy findings. In all CVD patients the estimated stroke localization was within the volume of irradiation. There were no significant differences in the infarction/hemorrhage ratio ($P>0.3$), of lacunar or posterior circulation syndrome compared to middle cerebral artery syndromes with cortical features ($P=0.22$), or proportion of patients who died within the first month after stroke onset (60 % vs 59 %, respectively) between CVD patients and population controls. The main problem when interpreting these results was however, that the few cases and controls available gave a low statistical power, which excludes detection of differences that were not large.

An external cause of stroke, emanating from an embolus from a plaque-affected cardiac or carotid artery, may theoretically have contributed to the increased CVD mortality in previous cohort studies (2,14), which is in accordance with the results from Markussis et al (34), showing an increased prevalence of intima media thickening and plaques in the carotid arteries in this patient group. However, a recent cross-sectional study of all women with hypopituitarism, on conventional hormone treatment, but with unsubstituted GH deficiency, recruited from the same previous cohort (2), no increase in intima media thickening or number of plaques in the carotid arteries or of major cardiac

abnormalities was recorded (22). This would argue against an external cause and more in favor of a local cause for stroke in the present study group.

34.2. Surgical trauma and CVD.

Another possible explanation for the CVD deaths is the surgical trauma, as significant vascular changes have been documented in children operated for craniopharyngiomas [(50)35]. This is also in agreement with the finding of a higher risk for CVD accidents after debulking surgery in patients irradiated for pituitary adenomas [(2048)]. The epidemiological data evaluating this hypothesis are, however, meager. In a Swedish cohort, 95 % of the patients were operated via the transcranial route and only 5 % via the transsphenoidal route, which made it impossible to evaluate the impact of surgical technique for CVD risk. However, in the previous study (21), there was a similar extension of pituitary tumour growth, histological tumour diagnoses, and surgical approach in CVD and control patients [(2139)]. In the UK study by Tomlinson et al, [16] 317 patients were operated via the transcranial route and 410 via the transsphenoidal route, while 227 patients were not operated at all (14). Unfortunately, the authors do not present any risk estimates for cardiovascular mortality or CVD mortality with respect to surgery vs. no surgery or with respect to surgical route. . These results are also in accordance with the study from Tomlinson et al (14) in which the operation regimens (transsphenoidal or transcranial) not had any significant impact on the increased mortality in patients with hypopituitarism. If anything, debulking surgery *per se* increases the risk of more extended hypopituitarism. Furthermore, occlusive arteriopathy in the form of Moya Moya disease,??? (may also occur as a result of a compression of the circle Willis by a slowly growing basal pituitary tumor (29).

34.3. *Hormonal dysfunction* *Hormonal dysfunction and CVD.*

Hormonal dysfunction may through various metabolic effects contribute to the enhanced risks for cardiovascular and CVD mortality observed in the epidemiological studies of patients with hypopituitarism and pituitary adenomas. Well-documented modifiable risk factors for CVD include hypertension, smoking, diabetes, hyperinsulinemia and insulin resistance, carotid stenosis, atrial fibrillation, dilated cardiomyopathy and valvular heart diseases [(Goldstein LB 2001).51] However, abnormalities in serum lipids have traditionally been regarded as a risk factor for coronary heart disease but not for CVD, but recent studies have shown that also the stroke risk can be reduced after treatment with cholesterol lowering drugs [(Goldstein 200151)].

Stroke emanating from an embolus from a plaque-affected cardiac or carotid artery, may theoretically have contributed to the increased CVD mortality observed in previous cohort studies [(2,143,16)], which is in accordance with the results from Markussis et al [(3452)], showing an increased prevalence of intima media thickening and plaques in the carotid arteries in this patient group. On the other hand, in a cross-sectional study of women with hypopituitarism on conventional hormone treatment, but with unsubstituted GHD no increase in intima media thickening or number of plaques in the carotid arteries were recorded, nor were any major cardiac abnormalities [(2217)].

A circumstantial evidence in favor of hormonal dysfunction as an important step in the causal chain leading to cardiovascular and CVD mortality, was the observation in one of the cohort studies that a significantly longer duration of symptoms for hypopituitarism before operation was recorded among females that later died of CVD [(Bülow et al39)].

4.3.1. GH deficiency and CVD

It has been shown that hypopituitary patients on conventional hormone treatment, but unsubstituted GHD, have a shortened life expectancy due to cardiovascular [(Rosen, Bulow, Tomlinson)3,15,16] and particularly CVD mortality [(Bulow, Tomlinson)3,16]). These findings are based on large cohort studies from both Sweden and the UK. Even if the conventional hormone treatment has differed somewhat among studies (e.g. different corticosteroids have been used, with cortisone acetate in the Swedish studies and hydrocortisone in the UK studies), the risk estimates were similar. These studies do not in themselves provide any evidence for that GHD is a main causal factor for the enhanced risk for cardiovascular and CVD mortality, because study designs and available data make it almost impossible to separate effects of GHD from that of other hormone deficiencies, CRT or surgical trauma. The claim from the authors of one of the UK studies that GHD did not contribute to the adverse overall prognosis [(14)16]), was unwarranted because the comparison, between 98 GHD patients and 13 patients without GHD, lacked reasonable statistical power [(Erfurth Lancet, Monson and Besser Lancet)53].

Hypopituitarism is another possible explanation for the CVD deaths and is a well-documented consequence of irradiation of pituitary adenomas or other brain tumors (15,16). Information on hypopituitarism has however, been missing in the majority of previous studies reporting stroke after radiotherapy for cerebral tumors (17-20). A novel observation in the recent study from Erfurth et al (21) was that among the female patients who died of CVD, and also had the highest SMR's for CVD deaths (2), a significantly longer duration of symptoms for hypopituitarism before operation was recorded. No such difference was seen among the males. Thus, it is possible that unsubstituted pituitary insufficiencies before operation, e.g. gonadal insufficiencies, contributed to this increased mortality.

There are, however, a number of clinical and experimental studies supporting that unsubstituted GHD impairs the cardiovascular risk factor pattern for the patients. These effects include lipid abnormalities, increase in fat body mass and reduction in lean body mass, high waist/hip ratio, insulin resistance, and vascular endothelial dysfunction [(9,1018,54)]. In a recent meta-analysis based on 37 clinical trials, GH treatment had beneficial effects on lean and fat body mass, total and LDL cholesterol, and diastolic blood pressure, and but reduced insulin sensitivity [(Maison et al 2004)55].

Thus, circumstantial evidence supports that GHD may contribute to the increased CVD mortality through enhancing an atherosclerotic process, but available epidemiological studies have not been able to separate out an effect of GHD from other risk factors.

3.3.1. GH deficiency and acromegaly.

ACROMEGALY AND CVD, NO INFORMATION ON GH DEFICIENCY (AYAK 2004).

NO DISCUSSION OF THE RISK FACTORS PER SE THAT IS STRONGLY

CONTRIBUTING TO STROKE RISK IN ACROMEGALY PATIENTS.

Causes of cerebrovascular disease in acromegaly

Information of radiotherapy has been missing in many previous mortality studies of patients with acromegaly (Orme 1998, Alexander 1980, Nabarro 1987). In the study from Bates (1993) and Bengtsson (1988) the majority (63 % and 53%, respectively) were irradiated and from Wright (1970), 19 % of the patients were irradiated. However, no evaluation of the impact of radiotherapy was provided in these studies.

Well-documented modifiable risk factors for stroke have been carefully evaluated in the general population (Goldstein LB 2001). These factors include hypertension, smoking, diabetes together with hyperinsulinemia and insulin resistance. Further, abnormalities in serum lipids have traditionally been regarded as a risk factor for coronary heart disease but not for cerebrovascular disease (Goldstein 2001). However, recent studies have shown that the risk of stroke can be reduced after cholesterol lowering drugs (Goldstein 2001). Furthermore, asymptomatic carotid stenosis, and atrial fibrillation as other types of cardiac diseases, including dilated cardiomyopathy, valvular heart disease (e.g. mitral valve prolaps, endocarditis, and prosthetic cardiac valves) are well-documented modifiable risk factors for stroke. Overall an estimated 20% of ischemic strokes are due to cardiogenic embolism.

Hypertension is considered one of the most relevant negative prognostic factors in acromegaly, reported in one third of the patients (Nabarro 1987). However, control groups have been missing in most studies (review Colao). In a recent (unpublished) study of 200 patients with acromegaly, 40% of (based on diastolic blood pressure > 90 mm Hg) compared with 8% in a control population, had hypertension (review Colao). Further, the increased prevalence of insulin resistance and diabetes are also important risk factors for stroke in acromegaly (ref 169, 170). Untreated acromegaly is exposed to elevated levels of triglycerides, apolipoprotein (Apo) A-1 and Apo E, fibrinogen, plasminogen activator inhibitor activity, and tissue plasminogen activator (ref 21). Rhythm disturbances, such as ectopic beats, paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia, sick sinus syndrome, ventricular tachycardia, and bundle branch blocks are more frequently recorded, mainly during exercise, in acromegaly (Ref Colao, Kahaly 1992, Rodrigues 1989). In a recent study a high prevalence of both mitral and aortic valve dysfunction was recorded in patients with active acromegaly (Colao 2003). Left ventricular hypertrophy is found in most patients with acromegaly with the development of cardiomyopathy (21), followed by

impairment in diastolic and systolic cardiac function (137). Thus, there seem to be convincing evidence, based on cardiovascular risk factors, for the increase in cerebrovascular disease in patients with acromegaly.

34.3. 23. Other hormonal dysfunctions and CVD (estrogen and steroids).

Tomlinson et al [16] showed that patients with untreated gonadotropin deficiency was an independent significant factor affecting mortality. They had increased “vascular” mortality (SMR 2.85, 95 % CI 1.92-4.24) as compared with those with treated deficiency (SMR 1.23, 95 % CI 0.76-2.00) (14). The negative impact of untreated gonadotropins deficiency remained in multivariate internal analyses; however this was assessed only for overall survival. In patients with hypopituitarism (14).

Why were women more affected than men? The smaller vessel diameter in women might be of importance for the higher stroke risk for females in these cohorts (2,14). This idea has been suggested as an explanation for the increased risk of complications after carotid surgery in women compared to men (36).

Gender difference.

In the first Swedish cohort study with hypopituitarism, a higher risk for women than in men was indicated (Rosen & Bengtsson). The increased risk for women (women, SMR 2.39 and males, SMR 1.54) was also seen in the second Swedish cohort study with hypopituitarism. Also for cerebrovascular mortality females were at a greater risk (SMR 4.91) than males (SMR 2.64) (Figure 1). Finally, the latest study from the UK, included 1014 patients with hypopituitarism, in which univariate analyses indicated that mortality was also higher in women (SMR 2.29, 95% CI 1.86-2.82 vs males, SMR). In the group of patients with

nonfunctioning pituitary adenomas (n=573) as the underlying cause of hypopituitarism, excess mortality was explained by an increase in respiratory and cardiovascular deaths and was also increased in women compared to men.

Why were women more affected than men? The smaller vessel diameter in women might be of importance for the higher stroke risk for females in these cohorts (2,14). This idea has been suggested as an explanation for the increased risk of complications after carotid surgery in women compared to men (36).

Another possibility is the recent findings in menopausal women on estrogen substitution and who have not hypopituitarism, may be at higher risk for stroke compared to placebo (WHI).

5. Other causes of stroke

An external cause of stroke, emanating from an embolus from a plaque-affected cardiac or carotid artery, may theoretically have contributed to the increased CVD mortality in previous cohort studies (2,14), which is in accordance with the results from Markkussis et al (34), showing an increased prevalence of intima media thickening and plaques in the carotid arteries in this patient group. However, a recent cross-sectional study of all women with hypopituitarism, on conventional hormone treatment, but with unsubstituted GH deficiency, recruited from the same previous cohort (2), no increase in intima media thickening or number of plaques in the carotid arteries or of major cardiac abnormalities was recorded (22). This would argue against an external cause and more in favor of a local cause for stroke in the present study group.

6. Evaluation of stroke in patients with pituitary adenomas

In a recent study (21) on patients operated and radiated for pituitary tumours, an attempt to further elucidate the background mechanisms of stroke, the infarction/hemorrhage ratio, type of clinical stroke syndrome and time to death after stroke was made. This cohort included 342 patients operated and irradiated for pituitary tumors between 1952 and 1996, and 31 patients had died from CVD (CVD patients). Potential control patients who had died from CVD, matched for age, calendar year of death, gender, and hospital code, were randomly selected from the general population (population controls), with use of the cause-of-death register. The Oxfordshire Community Stroke Project (OCSP) classification was used to classify them into four different *clinical stroke syndromes* (33). The *type of stroke* (infarction or hemorrhage) was based on computerized tomography (CT), angiography, or autopsy findings. In all CVD patients, the estimated stroke localization was within the volume of irradiation. There were no significant differences in the infarction/hemorrhage ratio ($P>0.3$), of lacunar or posterior circulation syndrome compared to middle cerebral artery syndromes with cortical features ($P=0.22$), or proportion of patients who died within the first month after stroke onset (60 % vs 59 %, respectively) between CVD patients and population controls. The main problem when interpreting these results was however, that the few cases and controls available gave a low statistical power, which excludes detection of differences that were not large.

65. Conclusions (balanced).

Available epidemiology support increased mortality rates in cardiovascular diseases (1.5 to 4-fold higher) and CVD (2 to 8-fold higher) among patients with acromegaly. The literature gives, however, no clear picture of whether treatment modalities or longstanding excess of GH secretion are most important as risk factors for the enhanced mortality. A post treatment decrease of GH levels to 1-2 $\mu\text{g/l}$ seems to counteract cardiovascular mortality, but the impact on CVD mortality has not been assessed.

Also patients with other pituitary tumors or hypopituitarism have enhanced risks for cardiovascular mortality (1.5 to 2-fold higher) and CVD deaths (2.5 to 3-fold higher). Especially patients with craniopharyngiomas seem to have extremely high risks for CVD. Moreover, female patients with pituitary adenomas or hypopituitarism seem to be at higher risk for CVD than male patients.

Experimental data, clinical studies and case reports clearly support the potential impact of CRT, surgical trauma and hormone insufficiencies, including GHD, as risk factors for CVD deaths among patients with pituitary adenomas or hypopituitarism, but the epidemiological studies performed up to now have not been able to distinguish between the relative importance of these factors. There is presently no direct proof that GH replacement will decrease the increased risk for cardiovascular or CVD mortality. However, many vascular risk factors can be improved by GH replacement, which gives some hope that such therapy may increase longevity in this patient group.

The cohort studies already performed cannot separate the importance of possible cardiovascular risk factors associated with hypopituitarism, such as GH deficiency, excess substitution with glucocorticoids or other unphysiological hormone substitutions, or cranial irradiation. There is presently no direct proof that GH replacement will decrease the increased risk for cardiovascular mortality. However, many vascular risk factors can be improved by

GH replacement, which gives some circumstantial evidence that such therapy may increase longevity in this patient group.

The cerebrovascular mortality is increased more than the cardiac is true, but nevertheless radiation cannot be the cause of the increased cardiac mortality, or?

Radiation.....

In the Tomlinson's paper the causes of cardiovascular mortality was 60 cases vs 33 expected (excluding cerebrovascular mortality). Thus, this group contains all other manifestations of CV mortality but, cerebrovascular (SMR 1.82 $p < 0.0001$) I cannot see that these manifestations are caused by XRT.

An attractive hypothesis, for the increased risk in CVD disease is an interaction between the longstanding consequences of unsubstituted hypopituitarism before diagnosis of a pituitary adenoma or inadequately substituted pituitary insufficiencies or GH deficiency together with the effect of radiotherapy, affecting the cerebrovasculature. More studies are highly warranted with e.g. investigating type of stroke, clinical stroke syndrome, for understanding the background mechanisms of CVD in this patient group. Of importance is also that young age at diagnosis carries a considerable increased risk for cardiovascular mortality in this patient group, which makes early diagnosis very important. More studies are highly warranted (e.g. investigating type of stroke, clinical stroke syndrome), for understanding the background mechanisms of CVD in this patient group.

EXTRAS: The incidence of non-fatal vascular disease has hitherto only been assessed in females with hypopituitarism and unsubstituted GH deficiency (22). Compared to controls recruited from the general population, and matched for sex, age, smoking habits, educational level, and residence, an increased relative risk (RR) for cardiovascular incidence (3.7; 95% CI 1.2-11.3) was found, including both cardiac and cerebrovascular diseases. Furthermore, the consumption of cardio-active drugs was also significantly higher in patients than in controls.

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Legend Figure 1. Legend

Relative risk for mortality due to cardiac and cerebrovascular diseases in 344 male and female patients with pituitary insufficiency. The calculations are based on 4543 person-years at risk during the period 1952-1992. The Standardized Mortality SMR values are point estimates with 95% confidence intervals.

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LEGENDS

Figure 1. Hypothetical causal chains of events for risk factors for cerebrovascular disease among patients with acromegaly.

Figure 2. Hypothetical causal chains of events for risk factors for cerebrovascular disease among patients with pituitary adenomas (except acromegaly) and hypopituitarism.

Figure 3. Relative risk for mortality due to cardiac and cerebrovascular diseases in 344 male and female patients with pituitary insufficiency. The calculations are based on 4543 person-years at risk during the period 1952-1992. The Standardized Mortality (SMR) values are point estimates with 95% confidence intervals. Adapted with permission from [3].

Figure 1.

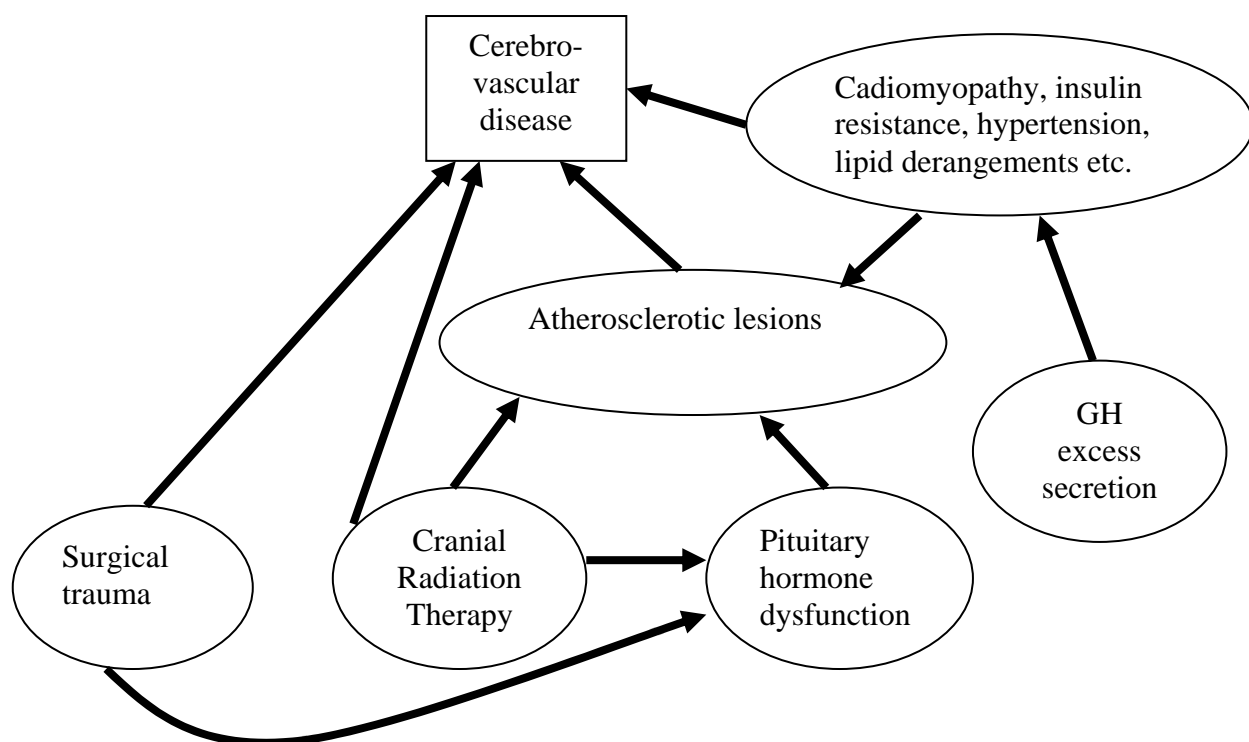


Figure 2.

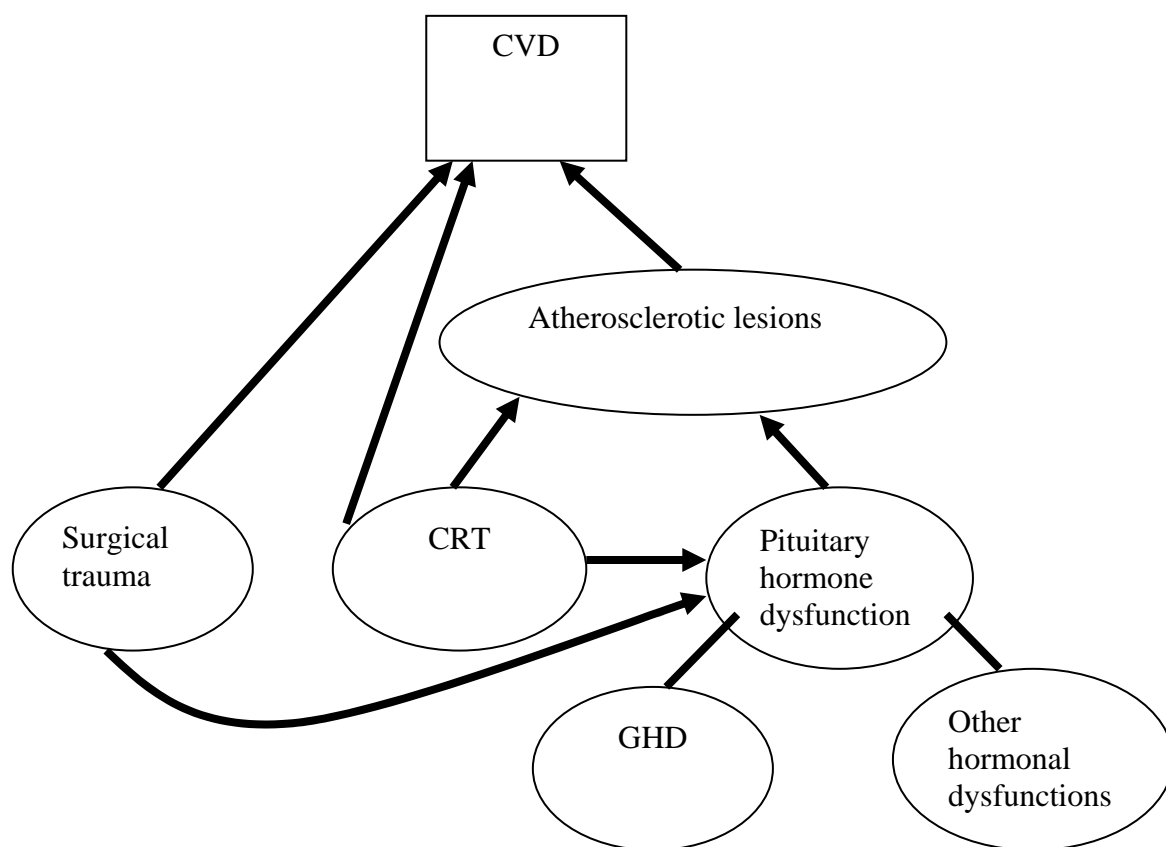


Figure 3

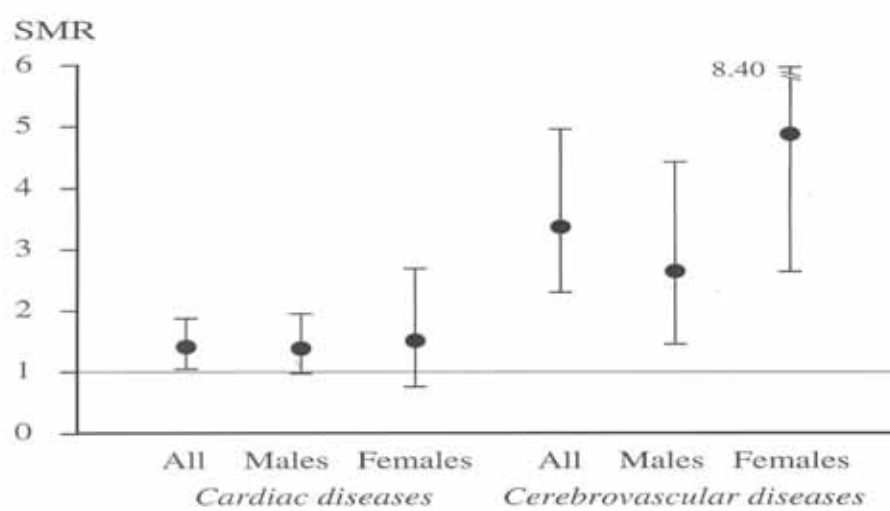


Table 1. Characteristics in number of patients, type of tumour, percentage of patients with operations or radiation, calendar year of inclusion for each study, average age of the patients at inclusion, median follow up (years) number of deaths during the follow up excluding deaths within the first postoperative month, for the five retrospective mortality cohorts of patients with hypopituitarism and pituitary adenomas (except acromegaly).

	Rosén & Bengtsson 1990	Bates et al, 1996	Bülow et al, 1997	Bates et al, 1999 ^a	Tomlinson et al, 2001
Number of patients	333	172	344	335	1014
Patients with pituitary tumors (%)	77	76	100	100	79
Patients operated for pituitary tumors (%)	61	79	100	100	77
Postoperative irradiation (%)	48	59	88	28	35
Calendar-year of inclusion in the study (range)	1956-1987	1967-1993	1952-1992	1970-1991	1941-2000
Average age at inclusion	47	52	52	48	45
Median follow up time (years)	15.2	Not given	11.9	10	12
Number of deaths	104	60	188	70	181

^ahypopituitarism not the inclusion criterion.

Table 2. Radiation therapy and symptom duration of hypopituitarism in patients who died from cerebrovascular disease (CVD patients), and control patients who did not die from cerebrovascular disease in a cohort of 342 patients with operated and irradiated pituitary tumors, 1946-1988. Adapted with permission from [(2139)].

	CVD patients (N=31)		Control patients (N=62)		P-value
	<i>median</i>	<i>range</i>	<i>median</i>	<i>range</i>	
Max absorbed dose (Gy)	45	(37-59)	42	(34-56)	0.26
Absorbed dose Centr (Gy)	41	(33-54)	40	(30-50)	0.24
Max BED (Gy ₃)	81	(60-116)	74	(60-99)	0.07
BED centr. (Gy ₃)	67	(48-98)	67	(43-83)	0.23
# of fractions	24	(9-44)	24	(12-36)	0.69
Field size (mm ²)	25	(10-49)	25	(16-36)	0.13
Radiation therapy					
200 KV X-rays	17		32		-
Cobalt or 8-33 MV X-ray	14		30		-
Symptom duration of hypopituitarism (months)	22	(0.5-180)	12	(0-156)	0.05

