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Incidence of myocardial infarction and stroke in acromegaly patients: results from the German Acromegaly Registry

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Abstract
Purpose Acromegaly is a rare disease generally brought about by a benign tumour in the pituitary and characterized by growth hormone (GH) and insulin-like growth factor 1 (IGF-1) excess. Increased mortality has been related to cardiovascular events that could be linked to these hormones and patients suffer from high rates of diabetes and hypertension. In this study, we examine if the incidence of myocardial infarction (MI) and stroke differ from that of the general population.
Methods Data from the German Acromegaly Registry in seven specialized endocrine centres were analysed (n = 479, 56% female, 46 years old at diagnosis, 5549 person-years from diagnosis). Standardized incidence ratios (SIR) were calculated as compared to the general population.
Results MI and stroke incidences were very close to those of the general population with an SIR (95% CI) of 0.89 (0.47–1.52, p = 0.80) for MI and 1.17 (0.66–1.93, p = 0.61) for stroke. Acromegaly was uncontrolled in 16% of patients with MI or stroke versus 21% in those without (p = 0.56). Prevalence of hypertension at the initial visit was much higher in those with MI or stroke than those without (94 vs. 43%, p < 0.001). No association was seen between radiation therapy and stroke.
Conclusions For acromegaly patients being treated at specialized centres, the incidence of MIs and strokes does not seem to differ from the general population. Certainty regarding such statements requires large, prospective studies however.

Keywords Acromegaly · Myocardial infarction · Heart attack · Stroke · IGF-I · Growth hormone

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Introduction

Acromegaly is characterized by growth hormone (GH) excess, which is most often caused by a GH-secreting pituitary adenoma. The disease is associated with increased mortality due primarily to cardiovascular (and cerebrovascular) events that may be directly related to GH and/or consecutive insulin-like growth factor-1 (IGF-1) excess [1–3].

Acromegalic cardiomyopathy is a typical and frequent complication of chronic GH-excess, which is characterized by concentric biventricular hypertrophy, impairment of diastolic function and mitral and aortic valve disease [4–7]. In addition, coronary artery disease (CAD) may contribute to the cardiac phenotype in acromegaly patients as suggested by early pathological studies [7–10]. Coronary risk factors like hypertension, insulin resistance and diabetes mellitus are frequent complications of acromegaly, thus providing a possible link between GH hypersecretion and CAD [1, 6, 11]. Furthermore, GH and IGF-1 excess may themselves

cause functional and morphological vascular alterations to some extent [12, 13]. On the other hand, there are studies questioning an increased prevalence of CAD in patients with acromegaly or even suggesting an antiatherogenic effect of GH-IGF-1 excess [10, 14]. In one cross-sectional study, the evaluation of the Framingham risk score and coronary artery calcium as assessed by CT showed that 41% of acromegaly patients were at risk for atherosclerosis [15]. The control of acromegaly, however, did not influence the extent of coronary atherosclerosis and the study provided indirect evidence that calcium deposits may not progress in acromegaly as in the general population, which would be consistent with a protective effect of GH-excess. In a prospective study, the risk of CAD was low and none of the acromegaly patients developed a major cardiac event during the 5 year study period [16]. A second prospective study also showed that the Agatston coronary artery calcium score is lower in acromegaly patients compared to the general population and did not change substantially over a period of almost 5 years [17].

Vascular risk factors like hypertension, insulin resistance and diabetes mellitus also predispose to cerebrovascular events, whose incidence was found to be increased in acromegaly patients by many researchers [18–23]. Moreover, radiotherapy may be another or additional predisposing factor, though there is disagreement pertaining to a potential association between radiation treatment and cerebrovascular accidents. One early study did not see clear evidence of increased incidence and was unable to find an association with radiation therapy [24].

In all, the data on cardio- and cerebrovascular events in acromegaly are limited, controversial, mainly refer to older pathological studies or are based on mixed patient populations comprising controlled and uncontrolled acromegaly [1, 6–10, 15, 16, 25]. Hence, we decided to study the incidence of myocardial infarctions (MIs) and strokes along with the connection to radiation therapy in a well-controlled, representative and large cohort of patients from the German Acromegaly Registry.

Subjects and methods

German Acromegaly Registry

As part of an ongoing and evolving project, the German Acromegaly Registry collects data on acromegaly patients from 57 specialized endocrine centres, spread throughout all of Germany and which was described in detail elsewhere [26]. The data were collected retrospectively until 2003, when prospective collection began. The protocol for the data registry was approved by the Ethics Committee of the Charité-Universitätsmedizin Berlin, Germany, and by the Berlin commissioner for data protection and freedom of information.

Beginning on January 1, 2010, centres from Erlangen, Leipzig, two in Munich, Oldenburg, Stuttgart and Wiesbaden were selected to collect more detailed information on their patients. These centres were selected since they were active in data acquisition, contain about 20% of the patients in the registry and cover a large geographic region in Germany. The patients are representative for the whole registry regarding sex, age, age at first diagnosis, the proportion that received operations, the proportion on medication and the proportion with uncontrolled acromegaly, cf. [27]. Data on cardiovascular events were obtained by conducting interviews by phone, in person or referring to medical records. Hypertension, diabetes and dyslipidemia were defined by use of medication or previous diagnosis. Diagnosis could be made in the participating specialized endocrinology clinics based on systolic or diastolic blood pressure ≥140 or ≥90 mmHg respectively (hypertension), fasting blood glucose ≥7 mmol/l, random or 2 h OGTT glucose ≥11.1 mmol/l or HbA1c ≥6.5% (diabetes) and total cholesterol ≥240 mg/dl, HDL ≤40 mg/dl, LDL-cholesterol ≥160 mg/dl or triglycerides ≥200 mg/dl (dyslipidemia).

General population used for comparison

The determination of standardized incidence ratios (SIRs) requires information on rates of events as they depend on age and sex in an appropriate population. Incidence of MI was taken from the website of The Information System of the Federal Health Monitoring of Germany accessed in February 2016 (http://www.gbe-bund.de), which provides current data on acute MIs taken from the MONICA/KORA registry, where information on methodology has been provided elsewhere [28]. The MONICA study is headed by the World Health Organisation and is the world's largest study of hearth disease [29]. The incidence of stroke is based on the Ludwigshafen Stroke Study, which fills the gap of scarce epidemiological data on stroke in Germany [30]. The prevalence of smoking in Germany by age and sex was taken from the Robert Koch Institute's 2003 Telephone Health Survey, available from the website above and where information pertaining to design and methods can be found in previous publications [31]. The prevalence of diabetes by age was taken from the representative German "DEGS1" survey [32] and for hypertension from the DETECT study [33].

Statistical analysis

All MIs and strokes that took place no earlier than 8 years before diagnosis of acromegaly were included in the analyses. The choice of this time span was based on estimates suggesting that onset of the disease is about 8 years prior

to diagnosis on average [34, 35]. SIRs were estimated by dividing the number of observed events by the number of expected events, where the number of expected events was calculated as the sum of events in the general population for the given sex and age category over the observed age-span for that particular patient. The initial time point was taken to be diagnosis of acromegaly or an event, whichever came first. The Poisson confidence interval (CI) was used for the SIR based on the chi-squared distribution [36] and p values were found by inverting the CI.

As a sensitivity analysis, the effect of eliminating one centre with a relatively large number of missing data was explored and the repercussions of assuming that those with missing data had had events was also taken into consideration.

Group comparisons of metric variables made use of the *t* test with Welch's approximation and comparisons of count data made use of a chi-squared test without Yate's continuity correction, or a Fisher test if expected counts were below 5. Cochran–Mantel–Haenszel's test was used to compare count data for a range of age categories. All analyses made use of the software R version 3.1.2 and results were defined to be significant for $p \leq 0.05$.

Results

A total of 516 patients were found in the acromegaly registry from the centres considered here and data on MIs and strokes were available for 479 (92.8%) of them. Only one centre had more than 8% missing data and only one event was discounted for having occurred long before diagnosis of acromegaly, a MI at age 29, 35 years before diagnosis of acromegaly.

The characteristics of patients according to whether or not they had had a MI or stroke are presented in Table 1. As to be expected, those with an event were considerably older than those without. A pronounced difference can also be seen between the groups in the percentage of patients at the initial visit with high blood pressure. This difference remains almost unaffected by taking differences in age at diagnosis between the two groups into account. The number of patients who did not receive an operation is lower for those with MI or stroke, presumably because operations are not performed quite as often in older patients: the age at diagnosis for patients who received an operation (45 ± 14 years) is much lower than for those who did not (59 ± 15 years), $p < 0.001$.

Incidence of MI and stroke

Patients were observed for 11.6 years on average for a total of 5549 person years. A total of 13 MIs in 12 patients were observed, which occurred 10 years after diagnosis of acromegaly on average (range 1 year before diagnosis to 35 years after) and one of which was fatal. There were 15 strokes in 15 patients (one fatal), where one of the patients had also had a MI and the mean time lapse between diagnosis of acromegaly and stroke was 14 years (range 4 years before diagnosis to 35 years after). Figure 1 provides the SIRs for MI and stroke and demonstrates that the incidences observed in this study do not differ from those of the general population. As a sensitivity analysis, the data from the centre containing most of the missing data (78%) were discounted. The remaining data contain eight MIs leading to an SIR of 1.00 (95% CI 0.43–1.96, $p = 1.00$) and six strokes, giving an SIR of 0.84 (95% CI 0.31–1.84, $p = 0.87$). As a further sensitivity analysis, we consider the minimum number of events in those with missing data that would result in significantly elevated SIRs. For MIs, an SIR of 7.7 would be necessary in the population with missing data to arrive at a total SIR of 1.54 (95% CI 1.00–2.28). For strokes, an SIR of 3.2 would be necessary in the population with missing data to find a total SIR of 1.71 (95% CI 1.05–2.65).

Cardiovascular risk

Data on smoking were available from three centres and 154 patients. There were 33 smokers (21%) and a comparison to the German general population taking into account sex and age yields a standardized ratio of 0.84 (95% CI 0.58, 1.19, $p = 0.38$). Acromegaly patients have a higher prevalence of hypertension compared to the normal population ($p < 0.001$) though the proportion of older patients with hypertension does not differ substantially from that in the general population (Fig. 2). For example, in our registry 61/92 (66%) patients aged 65–74 had hypertension compared to 60% in the DETECT study, $p = 0.23$. Diabetes prevalence in the cohort is around 20% (Table 1) and thus substantially higher than in the general population ($p < 0.001$) and sets in at a much younger age (Fig. 2) and at lower values for BMI. For example, the prevalence of diabetes in the general population in Germany for those aged 50–59 is 5.7% compared to 26/106 (25%) in our cohort. Data for medication related to further risk factors were available for anti-hypertensives and lipid lowering agents and are presented in Table 2.

Radiation therapy

Data on whether or not a patient received radiation therapy were available for 453 (95%) of the patients. Three of the 15 patients with a stroke (20%) had received radiation

Table 1 Population characteristics

	Patients with MI[a] or stroke (n = 26)	Patients without MI and stroke (n = 453)	All patients (n = 479)	p value[b]
No. of women[c]	15 (57.7%)	255 (56.3%)	270 (56.4%)	0.89
Age, years	69.1 ± 10.1	56.7 ± 14.4	57.3 ± 14.5	<0.001
Age at first diagnosis, years	49.7 ± 15.7	45.5 ± 14.5	45.7 ± 14.6	0.20
Height, cm	169.9 ± 9.2	173.2 ± 11.6	173.0 ± 11.5	0.13
Weight, kg	79.8 ± 15.0	85.4 ± 16.9	85.1 ± 16.8	0.12
BMI[d], kg/m^2	27.5 ± 4.0	28.6 ± 4.7	28.5 ± 4.7	0.28
Diabetes (initially)[e], *n* = 18\403	5 (27.8%)	70 (17.4%)	75 (17.8%)	0.34
Diabetes (last visit), *n* = 22\431	8 (30.8%)	88 (19.4%)	96 (20.0%)	0.16
High blood pressure (initially), *n* = 17\392	16 (94.1%)	170 (43.4%)	186 (45.5%)	<0.001
High blood pressure (last visit), *n* = 24\426	20 (83.3%)	198 (46.5%)	218 (48.4%)	<0.001
Received acromegaly operation, *n* = 26\443	21 (80.8%)	413 (93.2%)	434 (92.5%)	0.036
On acromegaly medication	10 (40.0%)	205 (46.2%)	215 (45.8%)	0.55
Received radiation therapy	6 (24.0%)	98 (22.8%)	104 (22.9%)	0.89
Random GH[f], ng/ml, *n* = 20\264	0.80 [0.39, 2.62]	0.96 [0.39, 2.31]	0.92 [0.39, 2.33]	0.89
≥2.5 ng/ml	5 (25.0%)	62 (23.5%)	67 (23.6%)	0.79
≥1.0 ng/ml	8 (40.0%)	132 (50.0%)	140 (49.3%)	0.39
IGF-1[g], ng/ml, *n* = 25\439	157 [116, 210]	184 [131, 257]	181 [130, 256]	0.14
IGF-1 normal	18 (72.0%)	315 (71.8%)	333 (71.8%)	0.98
Random GH and IGF-1, *n* = 20\259				0.40
GH normal[h]/IGF-1 normal[i]	9 (45.0%)	115 (44.4%)	124 (44.4%)	
GH elevated/IGF-1 normal	5 (25.0%)	66 (25.5%)	71 (25.4%)	
GH normal/IGF-1 elevated	3 (15.0%)	16 (6.2%)	19 (6.8%)	
GH elevated/IGF-1 elevated	3 (15.0%)	62 (23.9%)	65 (23.3%)	
Acromegaly uncontrolled[j], *n* = 25\428	4 (16.0%)	89 (20.8%)	93 (20.5%)	0.56

[a] *MI* myocardial infarction

[b] P values refer to the comparison of patients with or without MI/stroke

[c] Entries provided as counts (%), means ± SD or median [interquartile range]

[d] *BMI* body mass index

[e] The number of data available is provided for those with\without heart attacks and strokes

[f] Growth hormone (GH) values were only used for those not known to be on Pegvisomant and values at the last visit are reported

[g] *IGF-1* insulin-like growth factor 1

[h] GH <1 ng/ml for random GH or <0.4 ng/ml for OGTT values

[i] IGF-1 < upper limit of centre specific, age and gender matched reference range

[j] Uncontrolled: elevated GH and elevated IFG-1 if not using Pegvisomant or simply elevated IGF-1 if using Pegvisomant

therapy compared to 100 of the 438 (23%) without,[1] p = 1.00. Patients who received radiation therapy were currently 58 years old versus 56 for those who had not (95% CI for difference, −4.5 to 1.0 years, p = 0.20) and were treated with radiation 2.7 years after diagnosis. Those treated with radiation had been observed for an average of 10.5 years compared to 15.1.

Discussion

The incidence of MIs and strokes in the Germany Acromegaly Registry did not differ from that of the general population and there was no evidence for a relationship between strokes and radiation therapy. The former statement was verified in sensitivity analyses demonstrating that missing data cannot affect this result without presuming implausibly high incidence among the small group for whom data were unavailable.

Hypertension is known to be a major risk factor for cardiovascular disease and stroke [36]. In our study, the number of patients with hypertension both at the initial visit as

[1] The stroke status of one patient who received radiation therapy and had a MI is unknown. This leads tot he discrepancy between the 103 radiation patients analysed and the 104 presented in Table 1.

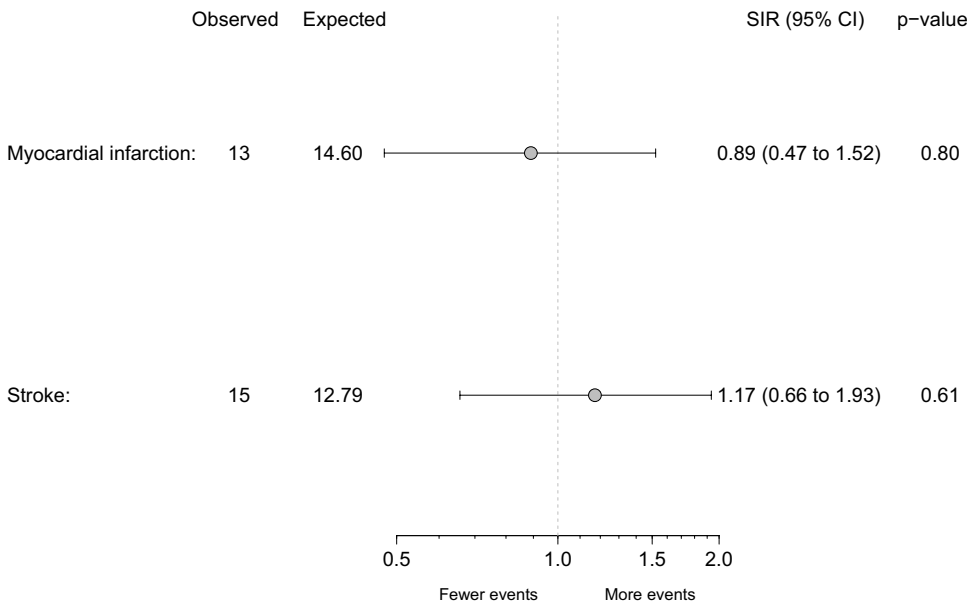

Fig. 1 Standardized incidence ratios (SIR) for myocardial infarction and stroke in acromegaly patients compared to the general population

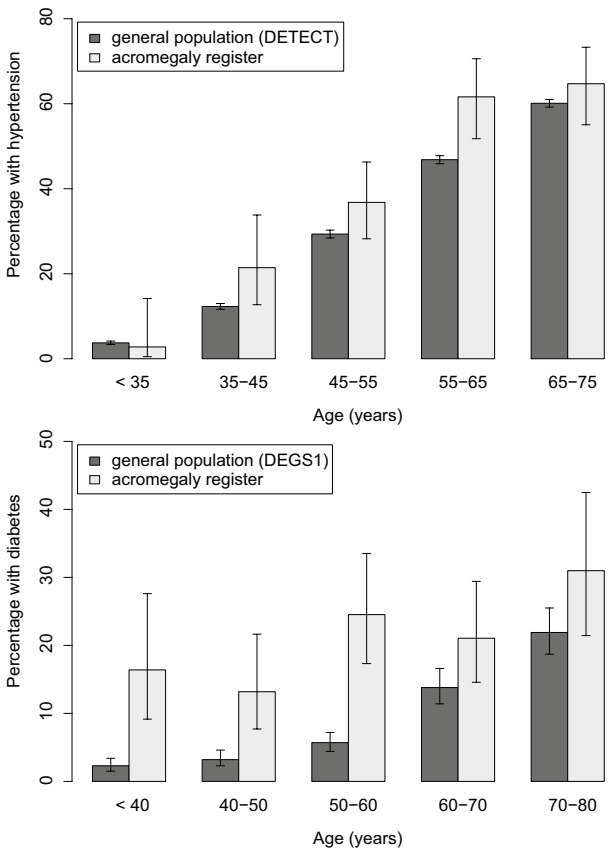

Fig. 2 Prevalence of hypertension (*upper panel*) and diabetes (*lower panel*) are compared between acromegaly patients and the general population by age

well as during follow-up are in line with observations from other studies [37], but significantly higher in the group of acromegaly patients with MI or stroke than in those without. Overall, however, the SIR for MI or stroke was not increased although the prevalence of hypertension was higher in the acromegaly patients when compared to the general population. One explanation might be the close monitoring at specialized clinics and resulting treatment of hypertension. Backing this up are the figures for the proportion of patients with hypertension on medication (82%, Table 2), which is significantly higher compared to the general population in Germany (67%, $p < 0.001$) according to the Gutenberg Health Study [38]. Alternatively, or in addition, the risk due hypertension may not be large enough to be detected with a relatively small number of events.

Diabetes is another important risk factor and also has a significantly higher prevalence among acromegaly patients, which might suggest that cardiovascular events should occur more frequently than in the general population. The prevalence of diabetes in our population (18%) corresponds extremely well to the observation from a Swedish registry (17%) [37]. Here, medication is used in only 57% of patients compared to roughly 75% in the general population [39], though disease control, BMI and duration of disease are important factors that can differ in our cohort from the population at large. The younger age and lower BMI values at which diabetes becomes manifest in acromegaly patients suggests strongly that the causal mechanisms and thus the association with cardiovascular risk could be different, which may explain the present results.

The prevalence of smoking was found to be comparable to the general population in a subset of the patients for whom data were available. Although data on lipid profiles are not complete in our cohort, the literature suggests that hyperlipidaemia rates are lower in patient with acromegaly, though HDL is also lower [40].

Table 2 Medication for those without myocardial infarction or stroke

	Count (%)
Anti-diabetics (among those with diabetes, $n=76$)	
On medication[a]	44 (57.1%)
On insulin	11 (14.3%)
Anti-hypertensives (among those with hypertension, $n=182$)[b]	
On medication	149 (81.9%)
Number of anti-hypertensives	
0	33 (18.1%)
1	52 (28.6%)
2	49 (26.9%)
≥3	48 (26.4%)
Lipid lowering agents[c] (among those with dyslipidemia, $n=93$)	
On medication	25 (26.9%)
On anticoagulants (data available for $n=416$ patients)	32 (7.7%)

[a]Data on medication were not available for 43 (9%) patients so numbers here can deviate from those in Table 1

[b]Hypertension and dyslipidemia include patients on medication for the disorder

[c]Two centres containing 216 (45%) patients were excluded, where these data were not available

The overall risk profile in patients with acromegaly might lead one to suspect that the chances of cardiovascular events should be high. However, it is hard to assess how well risk scores derived for the population at large apply to the rare disease acromegaly. The Framingham score for example is known to overestimate events in some populations, see e.g. [41].

The data presented here suggest that the incidence of hard clinical endpoints does not differ from the general population despite high risk status, at least in a well-treated population.

The association between radiation therapy and stroke that is sometimes postulated was not seen in our data. Given the small number of strokes, we cannot rule out the possibility of a connection, however. Moreover, those without radiation therapy were observed almost 5 years longer, which could have introduced a bias. Given evolving irradiation technology, relevant data will not be available for some time yet.

Our registry-based study has its weaknesses. Foremost, the collection of endpoint data from files and telephone calls is not comparable to a prospective design, but the endpoints MI and stroke were chosen in part to minimize this problem. Although more than 90% of the eligible population was analysed, missing data always harbours the potential for bias. With sensitivity analyses, we demonstrated however, that these data cannot change the general conclusions drawn here. In addition to patients that could not be included, certain parameters such as HDL-levels were not available at every centre meaning that various risk assessments such as SCORE cannot be performed [42]. It would be interesting to study how applicable such scores are to acromegaly patients and work toward identifying the risk factors appropriate for this rare disease. Finally, the choice of epidemiological data is not without drawbacks. Whereas the large MONICA study provides a basis for representative data on MI in Germany, an analogue for strokes is missing. The Ludwigshafen Stroke study provide the best data available in Germany despite the collection from a single city. Comparison with incidence from Western Europe is only marginally higher [30]. These shortcomings all suggest the need to explore cardiovascular risk in a prospective setting.

Conclusion

For acromegaly patients being treated at specialized centres, the incidence of MI and stroke does not seem to differ from the general population. Moreover, no association was found between stroke and radiation therapy. Certainty regarding such statements requires large, prospective studies however.

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Compliance with ethical standards

Conflict of interest CS has received lecture fees from Novartis, Ipsen and Pfizer and has served on advisory boards of Novartis and Pfizer. GS has served on advisory boards of Ipsen, Novartis and Pfizer. SS has received lecture fees from Novartis and Pfizer and has served on advisory boards of Novartis. JS has received lecture fees from Novartis, Ipsen and Pfizer and has served on advisory boards of Novartis and Ipsen.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol for the data registry was approved by the Ethics Committee of the Charité-Universitätsmedizin Berlin, Germany, and by the Berlin commissioner for data protection and freedom of information.

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