CLINICAL STUDY

Increased prevalence of acromegaly in a highly polluted area

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Abstract

Objective: Despite the contribution of national registries and population-based reports, data concerning the epidemiology of acromegaly is scanty. In addition, the role of the environmental context has not been investigated.
Design: Epidemiology of acromegaly was studied in the province of Messina (Sicily, Italy), focusing on the influence of environmental factors.
Methods: Four zones, characterized by different degrees of exposition to environmental toxins due to industrial pollution, were identified in the province: area A (76 338 inhabitants), area B (287 328 inhabitants), area C (243 381 inhabitants), and area D (47 554 inhabitants) at low, middle-low, middle, and high industrial density respectively. We identified all acromegalics who were born and resided in the province of Messina, among patients either referred to our endocrine unit or referred elsewhere but recorded in the archives of the provincial healthcare agency.
Results: In the province of Messina, we found 64 patients (2 in area A, 24 in area B, 28 in area C, and 10 in area D). Macroadenomas were 60%, the male/female ratio was 1, and mean age at diagnosis ($\pm$s.e.m.) was 45.4 ± 1.6 years. Overall, prevalence was 97 c.p.m. in the province (26 c.p.m. in area A, 84 c.p.m. in area B, 115 c.p.m. in area C, and 210 c.p.m. in area D). Risk ratio (RR), calculated in every area assuming area A as a reference, showed an increased risk of developing acromegaly in people residing in area D (RR = 8.03; $P < 0.0014$).
Conclusion: This study confirms the prevalence of acromegaly reported recently. The increased risk of developing this disease in area D suggests that the pathogenetic role of environmental context needs to be better evaluated.

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Introduction

Pituitary adenomas have historically been considered a low-prevalence disease and GH-secreting adenomas a rare occurrence. However, over the last three decades, besides studies on autoptic series, increasing neuroimaging investigations and population-based reports have shown that pituitary adenomas are the most frequent benign Central nervous system tumors with an estimated prevalence of at least 1/1064–1289 of the general population (1). Among pituitary tumors, prolactinomas are the most frequent, followed, in frequency, by nonfunctioning, GH-secreting, and ACTH-secreting adenomas.

In 1999, the known prevalence of acromegaly was $60/10^6$ inhabitants, according to the only four previous epidemiological studies reviewed by Holdaway (2). More recently, the setting up of national acromegaly registries in many European countries, some wide regional cross-sectional epidemiological studies (3, 4) and some case-finding studies based on biochemical screening (5),

allowed us to state that acromegaly is a disease less rare than previously thought and too often misdiagnosed or undiagnosed. To date, the estimated prevalence ranges from 36 to $151/10^6$ inhabitants, the mean age at diagnosis ranges from 41 to 48 years, and a slight female prevalence has occasionally been reported, although both genders seem to be equally affected (3–7).

In Italy, where a register of acromegaly has not yet been set up, the demography of the disease has not been investigated. Moreover, the Italian Government has identified some areas at high-risk for environmental crisis because of industrial pollution, one of which is located in the province of Messina. The aim of our study was to investigate epidemiological characteristics of patients with acromegaly in the province of Messina, one out of nine provinces in Sicily, focusing on the relationship between the geographical pattern of disease distribution and environmental context, given that the pathogenesis of the disease is largely unknown and the role of environmental factors is controversial.

Subjects and methods

The province of Messina lies in the Northeastern part of Sicily and is divided by a mountain ridge into two areas, overlooking the Tyrrhenian and the Ionian Sea respectively. The province includes a large urban center (the city of Messina) and other 107 small and medium towns, with an overall resident population of 654 601 inhabitants. The city of Messina is in front of the homonymous strait that connects the two seas (Fig. 1).

The Regional Agency for Environmental Protection (ARPA) is the institution committed to monitoring and surveying environmental pollution of our region. On the basis of the degree of exposition to environmental pollutants mostly due to industrial emissions, we identified four distinct zones in the province (Table 1): i) area A (the Ionian area, 31 towns, 76 338 inhabitants), low industrial density; ii) area B (the Tyrrhenian area, 71 towns, 287 328 inhabitants), middle-low industrial density; iii) area C (the city of Messina, 1 town, 243 381 inhabitants), middle industrial density; and iv) area D (5 towns, 47 554 inhabitants), high industrial density. Moreover, the last one has been identified by the National Government as a high-risk for health zone, because of an elevated concentration of industrial pollutants, especially, but not exclusively, of petrol–chemical origin.

The criteria to distinguish the four zones with a different degree of pollution have been based on environmental samples data – provided by ARPA – and were also related to industrial density. Air quality evaluation has been based on the measurement of the concentrations of the following compounds, whose maximal concentrations are defined by law: sulfur dioxide (SO_2), nitric dioxide (NO_2), nitric oxides (NO_x), carbon monoxide (CO), ozone (O_3), methane (CH_4), nonmethanic hydrocarbons (NMHC), and volatile organic compounds (VOC). Other causes of environmental pollution, not related to industrial emissions, contribute partially to the pollution burden.

Figure 1 Map of the province of Messina, 108 towns distributed in 4 zones characterized by different environmental context: i) area A (the Ionian area), 31 towns, low industrial density; ii) area B (the Tyrrhenian area), 71 towns, middle-low industrial density; iii) area C (the city of Messina), 1 town, middle industrial density; and iv) area D, 5 towns, high industrial density.

Table 1 Demography and environmental characteristics of the four zones identified in the province of Messina.

Area	Characteristics	No. of towns	Inhabitants
A (Ionian)	Low industrial density	31	76 338
B (Tyrrhenian)	Middle-low industrial density	71	287 328
C (City of Messina)	Middle industrial density	1	243 381
D (High-risk for health zone)	High industrial density	5	47 554
Province of Messina		108	654 601

We have identified all the acromegalics who were born and resided all their life in the province of Messina and were alive till 31 December 2008, by reviewing archives of our endocrine unit, Sicilian referral center for pegvisomant treatment, and of the Healthcare Agency of the province of Messina (Azienda Sanitaria Provinciale, ASP). In Italy, all acromegalics are recorded in the archive of the ASP to avail free medical benefits for follow-up of the disease.

In all cases, acromegaly was diagnosed according to the established criteria, i.e. increased serum insulin-like growth factor 1 levels and serum GH concentration >1 ng/ml after glucose (75 g, p. os) overload, in an appropriate clinical context. All identified acromegalic patients were requested to fill in a questionnaire on their lifelong residence to exclude migration. In the province, overall, and in every area, we calculated the prevalence of acromegaly and the male/female ratio of patients. In the group of patients referred to our unit, we evaluated mean age at diagnosis ($\pm$s.e.m.), prevalence of microadenomas and macroadenomas, and prevalence of adenomas occurring in a familial setting. Prevalence was calculated in accordance with current and accepted epidemiological criteria (8) and was expressed as cases per million of inhabitants (c.p.m). Data concerning the resident population were based on the last National Census Report (ISTAT 2001).

Risk ratio (RR) and 95% confidence interval (CI) were estimated with odds ratio method in area B (middle-low industrial density), in area C (middle industrial density), and in area D (high industrial density) assuming the population of area A, at low industrial density, as a reference. RR and 95% CI were also calculated in area D assuming the remaining part of the province (areas A+B+C) as reference.

Results

Among the acromegalics referred to our unit, we identified 55 patients (25 men and 30 women; mean age at diagnosis: 45.8 ± 11.5 years). At diagnosis, a pituitary macroadenoma was demonstrated in 39,

Table 2 Epidemiology of acromegaly in the four zones identified in the province of Messina.

Area	No. of acromegalics	Male/female	Macroadenoma (%)	Mean age (± s.e.m.)[a]	Prevalence (c.p.m.)
A	2	NC	50	NC	26
B	24	1.6	65	45.4 ± 2.1	84
C	28	0.6	70	44.9 ± 2.5	115
D	10	1.5	70	45.4 ± 3.5	210
Province of Messina	64	1	60	45.4 ± 1.6	97

NC, not calculated; both females, 34 and 64 years old.
[a]At diagnosis.

a microadenoma in 14, and a primary empty sella in 2 patients. Other nine acromegalics (six men and three women) were identified in the archive of the ASP.

Out of the 64 patients identified, 2 were born and resided in area A, 24 in area B, 28 in area C, and 10 in area D. Accordingly, the prevalence of acromegaly was 97 c.p.m. in the province of Messina overall, 26 c.p.m. in area A, 84 c.p.m. in area B, 115 c.p.m. in area C, and 210 c.p.m in area D. The mean age at diagnosis was 45.4 ± 1.6 years in the province of Messina, without significant differences in area B (45.4 ± 2.1 years), in area C (44.9 ± 2.5 years), and in area D (45.4 ± 3.5 years). In area A, the two patients were 34 and 64 years old when acromegaly was diagnosed. Overall, the disease was diagnosed before 30 years of age in 5.5% of patients. Concerning the male/female ratio, this was 1.0 in the province of Messina, 1.6 in area B, 0.6 in area C, and 1.5 in area D, while the two patients in area A were women. The prevalence of macroadenomas was 60% in the province of Messina, 50% in area A, 65% in area B, 70% in area C, and 70% in area D (Table 2).

In the group of patients referred to our endocrine unit, MEN 1 or familial isolated pituitary adenomas (FIPA) were diagnosed in two and four cases respectively. Regarding the two patients with MEN 1, one lived in area B and the other one lived in area C and regarding the four patients with FIPA, one resided in area B, one in area C, and two in area D. Germline mutations of *AIP* gene were searched for in all FIPA patients both by conventional DNA test and by multiplex ligation-dependent probe amplification, but genetic abnormalities were not found in any case. Data concerning these analyses were previously published elsewhere (9).

Assuming area A as a reference population, a significant increased risk of developing acromegaly was observed in area D with RR of 8.03 (95% CI 1.76–36.63; $P = 0.0014$) and in area C with RR of 4.39 (95% CI 1.05–18.43; $P = 0.0270$) but not in area B (RR = 3.19; 95% CI 0.75–13.49; $P = 0.0959$; Fig. 2). A significant increased risk of acromegaly was observed in area D with RR of 2.36 (95% CI 1.20–4.64; $P = 0.01$) also considering the remaining part of the province overall (areas A, B, and C) as reference (Fig. 3).

Discussion

In the absence of an Italian registry of acromegaly, our study aimed to provide reliable epidemiological data since our endocrine unit is considered a referral center for pituitary diseases in Sicily and Calabria, Southern Italy. Moreover, our analysis was implemented with data recruited from the archive of the ASP of Messina. It is possible, however, that a very small number of surgery-cured acromegalics, who were not followed up, could further increase the prevalence found.

One of the first papers concerning the demography of acromegaly was published by Alexander *et al.* in 1980 (10). In that study, conceived with a community-based approach, a disease prevalence of 38 c.p.m. was calculated in the Newcastle region (UK). A similar prevalence, ranging from 60 to 69 c.p.m., was reported a few years later in the studies carried out in Spain, Sweden, and Northern Ireland (11–13). During the last
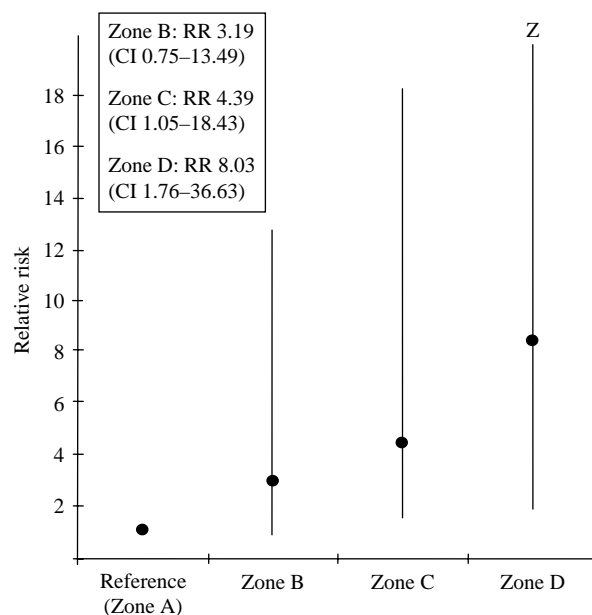

Figure 2 Relative risks and 95% confidence intervals (CI) for acromegaly in areas B (middle-low industrial density), C (middle industrial density), and D (high industrial density), assuming the population of area A (low industrial density) as a reference.
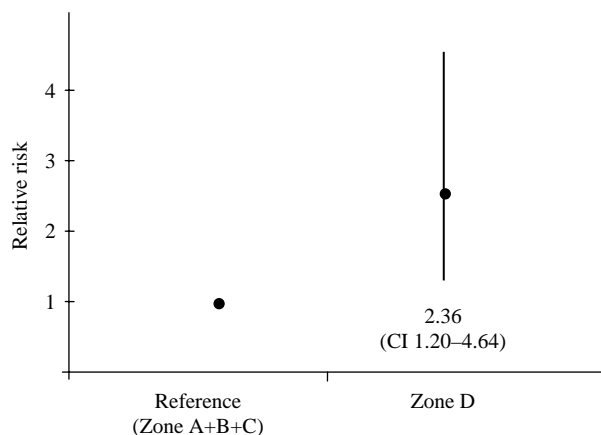
Figure 3 Relative risks and 95% confidence intervals (CI) for acromegaly in area D (high industrial density), assuming the sum of the populations of areas A, B, and C as reference.

decade, national registries of acromegaly have been instituted in many European countries, but they have failed to demonstrate that the prevalence of the disease was higher than previously calculated. Indeed, the studies based on the Spanish or Belgian registries of acromegaly estimated a disease prevalence ranging from 34 to 40 c.p.m. (6, 7). More recently, population-based reports, carried out in the province of Liege (Belgium) by Daly *et al.* (3) and in Bambury (UK) by Fernandez *et al.* (4) showed a higher prevalence of disease with 125 and 86 c.p.m. respectively. Nevertheless, the standardized incidence rate of acromegaly per 100 000 calculated in Northern Finland by Raappana *et al.* (14) was only 0.34.

The prevalence of acromegaly in the province of Messina, being about 97 c.p.m. overall, is largely comparable with those of other European countries, as reported in the most recent epidemiological studies. The demography of the condition in the four zones characterized by a different degree of exposition to environmental toxins showed a prevalence of 210 c.p.m. in area D, dramatically higher than previously reported. Area D includes 5 towns, hosts 47 554 inhabitants, and is officially identified as a high-risk zone for environmental crisis by the Department of the Environment of the Italian Government, because of the presence of an oil refinery, a steel plant, a thermoelectric power station, a lead recovery plant, and several small factories. Recently, on the basis of air pollutants distribution influenced by meteorological events, ARPA has suggested to include four neighboring small towns in the high-risk zone. In two out of these towns, we found a further three acromegalics, with the prevalence of disease reaching 238 c.p.m. In the air of area D, ARPA detected high concentrations of NMHC and of the following VOC: benzene, toluene, 1-3-butadiene, *trans*-2-pentene, 1-2-3-tribenzene, *cis*-2-butadiene, *trans*-2-butene, 2-methyl-1-pentene,

acetylene, α-pinene, β-pinene, cyclohexene, ethane, isobutene, isopentane, isopropilbenzene, met-cyclo-pentane, m-xylene, n-decane, n-nonane, p-dietil-benzene, o-etyltoluene, n-pentane, and n-octane. Despite the fact that this industrial settlement has been in the area for several decades, emissions and atmospheric concentrations of some of these pollutants were verified and ruled on only recently by specific laws. Moreover, no data is available yet concerning ground concentration of environmental pollutants. The Occupational Medicine Department of the University of Messina and the Osservatorio Epidemiologico Regionale, on the basis of regional hospitals' discharge forms, screened retrospectively the population living in this area for cancer burden and found that laryngeal, bone, and connectival tumors, among men, and all kind of tumors, among women, were more prevalent than in the population residing in surrounding towns in a 15 km radius area (15). The area D is the only zone of our province periodically monitored for pollution and screened for cancer burden. In the remaining areas, environmental pollution is not monitored because of a lower degree of pollution and a different type and distribution of industrial settlements.

Geographic clustering of pituitary adenomas has not been reported until now, even inside an area exposed to environmental toxics. In the population of Seveso (Lombardia, Northern Italy), Pesatori *et al.* (16) did not find a significant increase in prevalence of acromegaly after severe dioxine exposure, which occurred in 1976, but reported a tendency toward a higher risk of developing pituitary tumors overall. On the basis of the records of our endocrine unit, nonsecreting pituitary adenomas do not demonstrate a singular pattern of distribution (data not showed), and their prevalence and of the other types of pituitary adenomas are difficult to calculate because specific archives of the ASP are lacking.

The RR calculation in our province showed a significant increased risk to develop acromegaly in the population residing in the highly polluted area D, assuming the population of low polluted area A as a reference. RRs demonstrated a sort of gradient of decreasing prevalence of acromegaly related to a decreasing degree of pollution in the different zones (D > C > B > A), as shown by the finding of an increased relative risk also in area C, at middle industrial density. We have no information regarding cancer burden in area A and we have no explanation, at the moment, for the low prevalence of acromegaly in this area. However, these data could be explained either on the basis of a different environmental context or on the basis of a low 'acromegaly awareness' in area A. Nevertheless, the risk of acromegaly is significantly increased in area D even considering the cumulative population residing in areas A, B, and C as reference. Moreover, on the basis of ISTAT 2005 data, a different socioeconomic context affecting the prevalence of acromegaly in the four areas could be excluded, since the provincial medium incomes are

rather homogeneous ($\sim$14.500 € in area A, $\sim$14.200 € in area B, $\sim$20.800 € in area C, and $\sim$14.800 € in area D). Equally warranted is also the access to medical care as our province is divided into eight districts (on the basis of population and surface area) where hospitals and specialist outpatient clinics are hosted (supporting general practitioners): two hospitals/specialist outpatient clinics in area A (1/38 169 inhabitants/243 km^2), six in area B (1/47 888 inhabitants/391 km^2), four in area C (1/60 845 inhabitants/53 km^2), and one in area D (1/47 554 inhabitants/122 km^2).

Other epidemiological parameters investigated in our study did not differ significantly from previous reports (2, 6, 7, 17): male/female ratio is 1.0 in the province of Messina, with a male prevalence in area B and in area D and a prevalence of females in area C. The mean age at diagnosis did not vary among different areas, placing it in the fourth decade. Macroadenoma/microadenoma ratio is unbalanced to tumors $\geq$1 cm, as shown in other series, without significant local differences.

In conclusion, our findings confirm the more recent epidemiological reports of acromegaly, but the increased prevalence of the disease in the highly polluted area, not being explainable on the basis of a familial susceptibility or on a known genetic predisposition, suggests that the role of environmental factors in the pathogenesis of GH-secreting pituitary adenomas needs to be better evaluated.

Declaration of interest

Funding

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