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RESEARCH ARTICLE

Incidence of young-onset dementia in Italy: The Brescia register study

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The authors mourn the sudden loss of Dr. Luisa Benussi and would like to dedicate this article to her.

Abstract

INTRODUCTION: The goal of the present work was to assess the incidence of dementia with onset before the age of 65 years (i.e., young-onset dementia [YOD]) and define the frequencies of young-onset Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD), and dementia with Lewy bodies (DLB) in the general population.

METHODS: The study was conducted from January 1, 2019 to December 31, 2019 in Brescia province (population: 1,268,455). During the study period, all new YOD cases (incident YOD) were counted, and all patients' records reviewed. The incidence was standardized to the Italian general population in 2019.

RESULTS: A total of 29 YOD patients were diagnosed. The age-sex standardized incidence rate was 4.58 (95% confidence interval, 3.07–6.58) per 100,000 person-years. No difference in incidence rate between YOD due to AD or FTLD ($P = 0.83$) and between sexes ($P = 0.81$) was observed. YOD incidence increased with age, reaching its peak after 60 years.

DISCUSSION: Presenting neurodegenerative YOD phenotypes encompasses both AD and FTLD. Improved knowledge on YOD epidemiology is essential to adequately plan and organize health services.

KEYWORDS
Alzheimer's disease, frontotemporal dementia, incidence, population-based study, young-onset dementia

1 | BACKGROUND

Young-onset dementia (YOD) refers to onset of dementia before the age of 65 years.[1,2] Diagnosis of YOD is particularly challenging compared to late-onset dementia. It affects individuals in the midst of their careers, under employment, while raising families, and often with significant financial obligations. YOD diagnosis is usually delayed primarily because patients are not referred to dementia centers soon enough, and because health-care professionals may not initially take into consideration the fact that the cause may be a neurodegenerative disorder.[3–6] The focus of most dementia services is primarily upon the needs of older people, and as a consequence, these services are frequently unsuitable to respond to the specific needs of patients with YOD.[7,8] Finally, the costs of YOD involve not only the direct costs but also the indirect economic burden due to loss of employment and income.[9] From this perspective, understanding the epidemiology of YOD is the first step in addressing this challenge.

Revision of the clinical criteria for Alzheimer's disease (AD),[10] frontotemporal lobar degeneration (FTLD) spectrum,[11–14] and dementia with Lewy bodies (DLB)[15] has prompted a wider recognition of these disorders in experienced clinical settings. Concomitantly, the increased use of biological and imaging markers in routine clinical practice has further improved diagnostic accuracy of atypical clinical presentations.[16,17]

Thus, up-to-date epidemiological studies with register-based approaches and with the involvement of specific clinical experts could improve knowledge in terms of numbers and impact of YOD.[18–20]

Only a few studies have specifically assessed the incident rates of neurodegenerative YOD,[3,21–25] mainly in small population settings and using past clinical criteria. AD is reported as the most frequent form of YOD, followed by frontotemporal dementia (FTD),[3,21,24] but distribution estimates of different etiological diagnoses need to be investigated further.[26]

The above observations prompted the present study, which was based on the Brescia register, a consolidated collaborative network of dementia centers in Brescia province, Italy, with the following specific aims: (1) to assess the incidence of neurodegenerative YOD in the general population using new diagnostic criteria, and (2) to describe and compare the distribution frequencies of young-onset AD, FTLD, and DLB, to assess the most common young-onset neurodegenerative dementia.

2 | METHODS

2.1 | Study population

This study was conducted from January 1, 2019 to December 31, 2019 in Brescia province, located in Lombardy, northern Italy (area: 4785.62 km^2, population: 1,268,455, M/F: 0.97, ≥ 65 years of age: 38.00%; Italian National Institute of Statistics data, www.demo.istat.it). We considered all new cases of YOD confirmed in the study period, for people living in the reference geographical area, and reviewed all the patient records. For the purpose of the present study, we considered neurodegenerative dementia diagnoses, that is, AD, FTLD spectrum, and DLB. In this retrospective work, the study period dated to before the COVID-19 pandemic, to avoid biases in assessing incident diagnoses.

The Brescia register consists of a network including neurological and geriatric services and 11 Centers for Cognitive Disorders and Dementias (CCDD), involved in the care of cognitive disorders, covering all cases of dementia in the reference geographical area of Brescia province. CCDDs are a long-lasting and consolidated dementia network, operative since 2000; they provide care and promote awareness of dementia and actively collaborate with general practitioners (GPs). In Italy, every citizen has free access to health care through the National Health System. We further confirmed the inclusion of all eligible cases by contacting local lay associations and charities involved in dementia care.

2.2 | Assessment procedures

Each patient fulfilled clinical and imaging diagnosis for either AD, FTLD, or DLB, according to current clinical criteria.[10–15] Only patients with

YOD, namely dementia diagnosed ≤ 65 years old, were considered, that is, young-onset (YO)-AD, YO-FTLD, and YO-DLB.

Moreover, we considered FTLD subtypes, such as behavioral variant FTD (YO-bvFTD),[11] primary progressive aphasia (YO-PPA),[12] progressive supranuclear palsy (YO-PSP),[13] corticobasal syndrome (YO-CBS),[14] and frontotemporal dementia–amyotrophic lateral sclerosis (YO-FTD-ALS).[27] With regard to PPA subtypes, we considered both non-fluent variant PPA (nfvPPA) and semantic variant PPA (svPPA) belonging to the FTLD spectrum, while logogenic variant PPA (lvPPA) was considered under the AD group due to common etiology.[12] Unspecified FTD (uFTD) was defined when the FTLD subtype was still unclear.

The present study involved a two-step process: the suspected cases were first referred by GPs to CCDDs, based on symptom onset, an initial clinical and neuropsychological evaluation, and possible brain imaging study. The CCDD network allowed complete coverage of all suspected YOD cases, under the Italian National Health System, because all cases of suspected dementia must be referred to a CCDD. The CCDD staff are made up of neurologists or geriatricians with extensive experience in the field of dementia and primarily involved in the diagnosis and treatment of neurodegenerative dementing disorders.

Each referred patient with suspected YOD was then evaluated by the research team carefully recording demographic characteristics and family history and clinical features. According to the standardized protocol of the Italian National Health System, during the first visit, dementia experts performed general, cognitive, and behavioral examinations. Eligible patients underwent a standardized neuropsychological and behavioral evaluation as well as brain magnetic resonance imaging (MRI). Patients with both clinical features and pattern of brain atrophy fulfilling current criteria for AD, FTLD, or DLB[10–15] were considered in the present study. To further confirm clinical diagnosis, in selected cases, cerebrospinal fluid (CSF) analysis (tau, phospho-tau and amyloid beta42), functional imaging scan (positron emission tomography [PET] amyloid scan or brain fluorodeoxyglucose [FDG] PET scan or single-photon emission computed tomography dopamine transporter scan), or genetic screening for monogenic neurodegenerative dementias, were carried out as previously published.[18,28]

A detailed clinical history was carefully recorded through a structured questionnaire. We considered age at disease onset and time from onset to diagnosis. The age at onset was defined as the age at which the first symptoms consistent with YOD were observed by the partner or caregiver. Family history was computed by Goldman score.[29] Neuropsychological assessment included tests tapping global cognitive functions, specific cognitive domains, and behavioral disturbances, as previously published.[18,28]

At the end of the diagnostic work-up, based on clinical, neuropsychological, and instrumental data, if diagnosis of YO-AD, YO-FTLD, or YO-DLB was confirmed, the patient could be included in the study; otherwise, they were excluded. In doubtful cases, a further joint evaluation was carried out, with a resulting shared diagnosed reached via a team discussion. After agreement, the patient could be included if diagnosis was confirmed. Patients were followed-up for at least 2 years, and clinical diagnosis was confirmed.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources. The incidence of neurodegenerative young-onset dementia (YOD) and the frequencies of young-onset Alzheimer's disease (AD) or frontotemporal lobar degeneration (FTLD) in the general population remain challenging.
2. **Interpretation**: The age–sex standardized incidence rate of YOD was 3.71 (95% confidence interval, 2.48–5.33) per 100,000 person-years. Incidence rate of young-onset AD and young-onset FTLD was comparable. YOD incidence increased with age, reaching its peak after 60 years.
3. **Future directions**: Future multicenter and international studies are needed to improve knowledge on YOD epidemiology to adequately plan and organize health services.

2.3 | Statistical analysis

Categorical variables were reported as percentages, whereas continuous variables were reported as medians and interquartile ranges (IQRs). The crude YOD incidence rate was computed as the ratio between the number of incident YOD cases diagnosed in 2019 and the number of residents of Brescia province aged 30 to 65 years on January 1, 2019 (reference population, source: www.demo.istat.it). Assuming a fixed population structure during the 12 months of the study period, the reference population was considered an approximation for the number of person-years (PY) spent at risk by the reference population. Age, with predefined 5-year categories from 30 to 65 years, sex, and YOD-specific subtypes incidence rates were computed.

Incidence rates were directly standardized using the age and sex structure of the reference population and that of the general Italian population aged 30 to 65 years (source: www.demo.istat.it) to estimate the number of YOD incident cases in Italy, assuming the same incidence observed in the reference population. All rates were reported as the number of cases per 100,000 PY along with their 95% confidence intervals (CIs) computed through the Poisson exact method. Incidence rates were compared by testing the hypothesis that their ratio was equal to one (i.e., the null hypothesis). Statistical significance was set at P value ≤ 0.05. Statistical analyses were performed using R version 4.2.3.

2.4 | Standard protocol approvals, registrations, and patient consents

The study was approved by the Brescia Hospital Ethics Committee (NP5497) and by IRCCS San Giovanni di Dio Fatebenefratelli Ethics Committee, Brescia (N. 21/2023). The study was compliant with

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[30] and the Standards of Reporting of Neurological Disorders (STROND)[31] guideline requirements.

3 | RESULTS

3.1 | Participants

During the study period, 32 individuals with suspected YOD underwent initial assessment. At the end of diagnostic work-up, 3 individuals were excluded because they did not fulfil criteria based on the results of the comprehensive diagnostic work-up ($n = 1$ not fulfilling AD criteria, $n = 1$ not fulfilling FTLD criteria, $n = 1$ diagnosis of vascular dementia).

Thus, 29 YOD patients were diagnosed in Brescia province: YO-AD was diagnosed in 12 (41.38%) cases, YO-FTLD in 15 (51.72%) cases, and YO-DLB in 2 (6.90%) cases. Among those diagnosed with YO-FTLD, 5 patients (33.33%) were diagnosed as bvFTD, 4 patients (26.67%) as PPA (2 with nfvPPA and 2 with svPPA), 4 patients (26.67%) as extrapyramidal variants of FTLD (3 with CBS and 1 with PSP), and 2 patients (13.33%) as uFTD subtype. No cases of FTD-ALS were identified (see Table 1).

All YO-AD patients showed hippocampal atrophy on MRI, and in 7 out of 12 patients, diagnosis was further confirmed with amyloid markers (6 CSF analyses and 1 PET amyloid scan). FTLD patients had supporting diagnostic findings in 14 out of 15 cases: 5 patients carried pathogenetic FTLD-related variations (4 *Granulin* mutations and 1 *C9orf72* expansion), 5 patients tested negative for AD-related markers (3 CSF analyses and 2 PET amyloid scan), and 4 patients showed frontotemporal hypometabolism at brain PET-FDG. The two DLB patients underwent CSF analyses and AD-related pattern was ruled out. The demographic and clinical characteristics of YOD patients and diagnostic subtypes are reported in Table 1.

3.2 | Incidence rates of YOD in Brescia province and estimates of incidence of YOD in Italy

As reported in Table 2, the incidence rate of YOD was 4.55 (95% CI, 3.05–6.53) per 100,000 PY, while the age–sex standardized incidence rate was 4.58 (95% CI, 3.07–6.58) per 100,000 PY.

This incidence would yield an estimated 1476 (95% CI, 987–2124) YOD cases in the whole Italian population ignoring mortality, with an age- and sex-standardized incidence rate of YOD of 5.04 (95% CI, 3.37–7.25) per 100,000 PY in Italy.

3.3 | Incidence rates of YOD subtypes

The incidence rate for YO-AD was 1.88 (95% CI, 0.97–3.29) per 100,000 PY, while the age–sex standardized incidence rate was 1.90 (95% CI, 0.98–3.31) per 100,000 PY. Incidence rate for YO-FTLD was 2.35 (95% CI, 1.32–3.88) per 100,000 PY, while the age–sex standardized incidence rate was 2.37 (95% CI, 1.32–3.90) per 100,000 PY.

No significant difference was found in crude incidence or in age–sex standardized incidence between YO-AD and YO-FTLD ($P = 0.83$). Similarly, no significant differences between YO-AD and YO-FTLD rates emerged when excluding extrapyramidal FTLD variants ($P = 0.98$). The rarest form of YOD was DLB, with incidence rate of 0.32 (95% CI, 0.04–1.15) per 100,000 PY, and an age–sex standardized incidence rate of 0.31 (95% CI, 0.04–1.14) per 100,000 PY.

3.4 | Demographic correlates of incidental YOD

The median age at diagnosis of YOD was 62 years (IQR, 59–64.0), while the median interval between symptom onset and diagnosis was 2 years (IQR, 1–3). The youngest age at onset was 49 years in a patient with bvFTD. Fifteen incident cases (51.72%) were women and 14 (48.28%) were men; incidence rates for YOD were 4.75 (95% CI, 2.66–7.84) per 100,000 PY for women and 4.35 (95% CI, 2.38–7.30) per 100,000 PY for men, with no differences between groups ($P = 0.81$). YOD incidence increased with age, reaching its peak of 16.13 (95% CI, 9.03–26.60) cases per 100,000 PY in the 60 to 65 age group.

No significant differences between sexes by age groups were reported (see Figure 1A). Both YO-AD and YO-FTLD increased with age, with no differences between like age groups (see Figure 1B). When we considered age at disease onset, no significant differences between sexes by age at disease onset groups were reported (see Figure 1A), and both YO-AD and YO-FTLD increased with age at disease onset, with no differences between like age at disease onset groups (see Figure 1B).

4 | DISCUSSION

YOD patients and their caregivers have unique needs compared to those with late-onset dementia, but the impact of YOD is still under-researched.[32,33] In the present register-based study, we estimated the incidence rates of neurodegenerative YOD, considering YO-AD, YO-FTLD, and YO-DLB, and reported an incidence of ≈ 4.6 per 100,000 PY. Furthermore, we found a comparable incidence rate of YO-AD and YO-FTLD, ranging from ≈ 1.9 to 2.3 per 100,000 PY, while DLB was the rarest YOD disorder. Incidence rates increased with age, with the peak incidence of ≈ 16 per 100,000 PY in the 60 to 65 age group.

Compared to previous studies,[3,21–25] the present work has covered the largest source population for estimating the incidence of YOD; it has considered the revised criteria for AD, FTLD, and DLB;[10–15] took into consideration structural and functional brain imaging as well as amyloid markers in the diagnostic work-up; included the overall spectrum of FTLD phenotypes: and diagnoses were confirmed by dementia specialists. We also prevented excessive similarity to previous studies by considering the diagnostic subtypes under the YOD label: we specifically assessed the incidence rates of YO-AD, YO-FTLD, and YO-DLB, excluding cases with other rare causes of neurodegenerative disorders, such as Huntington's disease or Creutzfeldt–Jakob disease. This was

TABLE 1 Demographic and clinical characteristics of incident cases with young-onset dementia and subtypes at time of diagnosis.

Variable	All ($n = 29$)	YO-AD ($n = 12$)	YO-DLB ($n = 2$)	YO-FTLD ($n = 15$)	YO-bvFTD ($n = 5$)	YO-PPA ($n = 4$)	YO-CBS/PSP ($n = 4$)	YO-uFTD ($n = 2$)
Age at diagnosis, years	62.0 (59.0–64.0)	61.5 (58.0–62.0)	62.5 (62.2–62.8)	63.0 (61.0–64.0)	63.0 (63.0–64.0)	61.5 (58.8–63.5)	64.0 (63.8–65.5)	60.5 (59.8–61.2)
Sex, female %	52.0	42.0	0.0	67.0	60.0	75.0	75.0	50.0
Age at onset, years	60.0 (57.0–61.0)	59.5 (57.0–61.2)	60.5 (60.2–60.8)	59.0 (58.0–60.5)	59.0 (59.0–60.0)	59.0 (57.0–60.0)	62.0 (60.0–63.2)	58.5 (58.2–58.8)
Disease duration, years	2.0 (1.0–3.0)	1.0 (1.0–3.00)	2.0 (2.0–2.0)	3.0 (3.0–4.0)	3.0 (3.00–4.0)	2.5 (1.7–3.5)	4.5 (2.5–6.00)	2.0 (1.5–2.5)
Education, years	8.0 (7.5–11.0)	8.5 (8.0–12.5)	6.5 (5.8–7.2)	8.0 (6.0–9.5)	7.0 (5.0–8.0)	10.0 (7.25–12.5)	9.5 (7.25–11.5)	8.0 (8.0–8.0)
Family history (GS = 1 or 2), %	10.3	0.0	0.0	20.0	90.0	25.0	25.0	50.0
MMSE	23.5 (19.8–27.0)	24.0 (23.0–26.5)	21.0 (20.0–22.0)	25.0 (15.5–27.5)	25.0 (22–30.0)	20.5 (13.0–27.0)	27.0 (23.5–27.2)	17.0 (16.5–17.5)
Distribution of YOD phenotypes, %	–	41.4	6.9	51.7	–	–	–	–
Distribution of YOD FTLD, %	–	–	–	–	33.3	26.7	26.7	13.3

Note: Results are expressed as median (interquartile intervals) or numbers (percentage).

Abbreviations: AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; CBS, corticobasal syndrome; DLB, dementia with Lewy Bodies; FTLD, frontotemporal lobar degeneration; GS, Goldman score (see Methods for details); MMSE, Mini-Mental State Examination; PPA, primary progressive aphasia; PSP, progressive supranuclear palsy; uFTD, unspecified frontotemporal dementia; YO, young onset; YOD, young-onset dementia.

TABLE 2 Incidence rates of young-onset dementia by 5-year age groups (per 100,000 person years).

Age at diagnosis (years)	Cases	Incidence	95% CI
30–34	0	0.00	0.00–5.33
35–39	0	0.00	0.00–4.69
40–44	0	0.00	0.00–3.98
45–49	1	0.96	0.02–5.36
50–54	3	2.86	0.59–8.36
55–59	10	10.53	5.05–19.36
60–65	15	16.13	9.03–26.60
Total	29	4.55	3.05–6.53

Abbreviation: CI, confidence interval.

principally based on the existing organization and structure of the Italian National Health System, under which all suspected cases of YO-AD, YO-FTLD, and YO-DLB are referred to the CCDD, providing certain numbers of new diagnoses.

A relevant new finding of this study was that incidence rates of YO-AD and YO-FTLD were comparable, both considering only FTD subtypes (YO-bvFTD or YO-PPA) or even including YO-PSP/CBS phenotypes. This is contrary to previous research that claims that AD is the most frequent cause of YOD.[3,21–25] These findings may be partially ascribed to the increasing awareness of FTLD and its phenotypes, with better diagnostic accuracy over the years.[18,19] Indeed, the only study that assessed incidence rates of YOD considering reference population aged 30 to 65 years, but with previous diagnostic criteria, reported a clear-cut higher incidence rate of YO-AD (5.7 per 100.000 PY) compared to the present study, but with lower incidence rate of YO-FTD (1.3 per 100.000 PY) and even of YO-DLB (0.1 per 100.000 PY).[24] However, another study from Cambridgeshire assessing incidence rates of YOD in population aged 45 to 65 years, published with earlier clinical criteria, reported an increased but not that significant of YO-AD (4.2 cases per 100.000 PY) than YO-FTD (3.5 cases per 100.000 PY).[21] Indeed, geographical differences in YOD subtype incidence, also determined by genetic background, cannot be ruled out. Interestingly, as already demonstrated in the FRONTIERS study, a population-based register assessing incidence rates of the FTLD spectrum in Europe,[19,34] YO-FTLD also presented balanced phenotype distribution, with almost 40% of cases with bvFTD, 30% of cases with PPA, and 30% of cases with PSP/CBS phenotypes. Finally, as expected, DLB incidence rates in young adulthood were negligible.

There are several limitations and strengths of the study. Collecting incidence data is challenging but enables us to make the best esti-

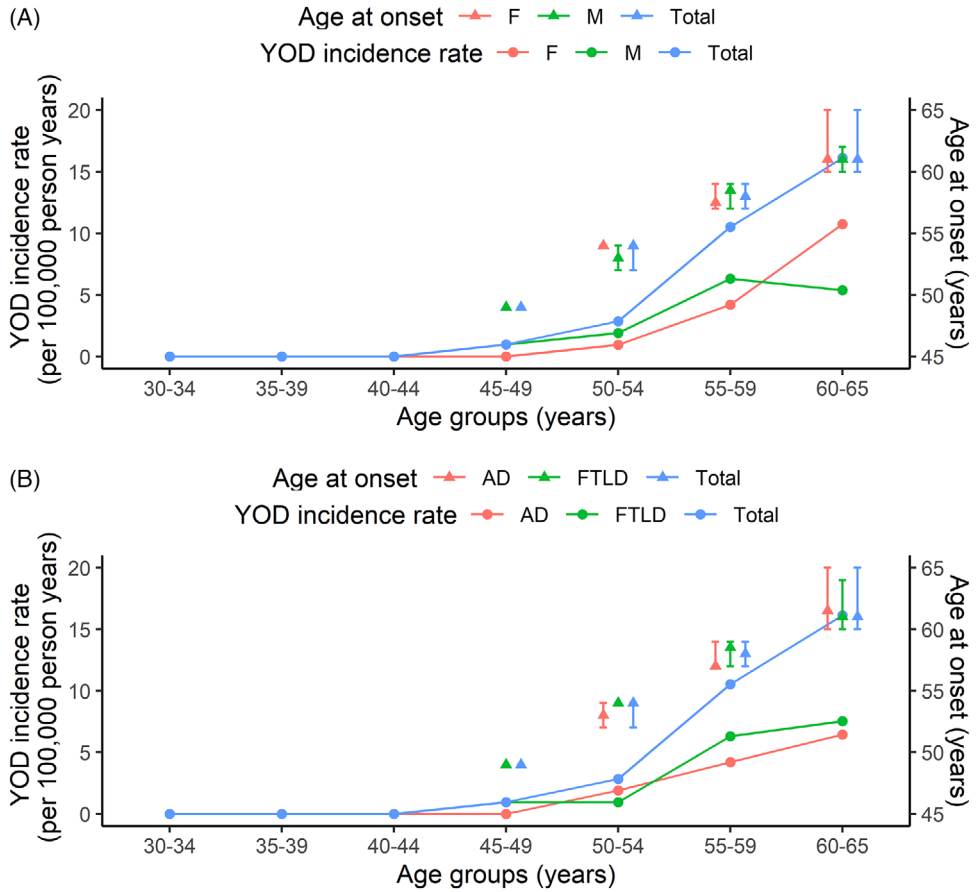

FIGURE 1 YOD age at onset and incidence by age groups and sex (A) and by age groups and phenotypes (B). AD, Alzheimer's disease; F, female; FTLD, frontotemporal lobar degeneration; M, male; YOD, young-onset dementia.

mate of the new burden of a disease per year in a specific population and to characterize the phenotype spectrum.[19] Therefore, we herein applied the reconstructed cohort-design approach,[35] and we specifically considered the general population aged between 30 and 65 years, which is key to assessing precise incidence rates according to our aims. However, we acknowledge that population-based registers require a number of years of activity to ensure that early biases are resolved; this is generally a bias toward enrollment of prevalent cases, wrongly classified as incident within the 1 year of the study.[36]

One possible limitation of our study is the potential underascertainment due to lack of referral by other neurologists, geriatricians, and psychiatrists to the multidisciplinary register, even though the capillary network of Brescia centers engaged in dementia care offers a unique advantage in a register-based approach. Another limitation is possible misdiagnosis; however, the comprehensive clinical evaluation, the imaging and biomarker assessment, although implementable, along with diagnostic confirmation at follow-up, makes this unlikely. Moreover, in this epidemiological study, we considered clinical diagnosis according to the revised criteria, but we cannot ascertain definitive biological, genetic, or final neuropathological diagnosis in all cases. Finally, generalization of these data should be taken with caution, and further YOD incidence studies should be conducted in other regions or countries to confirm the present findings. Collaborative work among multinational registries, studying different populations and ethnicities, should be the next step to improve our understanding of YOD. This will allow comparable methodological approaches to be adopted in terms of inclusion/exclusion criteria and reference populations, to strengthen YOD incidence rate results on larger population-based registries, to clearly define differences in incidence rates and eventually geographical diversities of YOD subtypes, and to implement knowledge of biological bases of YOD. Despite these limitations, the results of the present study highlight the need to raise awareness on YOD,[20,36] to promote appropriate public health service policies, design effective diagnostic algorithms, and define tailored treatment approaches for YOD cases.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

Anonymized data will be shared upon reasonable request by the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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