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Temporal trend of newly diagnosed type 1 diabetes children and adolescents identified over a 35-year period in a Brazilian institution

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ABSTRACT

Aims: To evaluate the temporal trend of newly diagnosed Type 1 Diabetes cases over a 35-year period in a reference Pediatric Endocrinology service in the city of Belo Horizonte, Brazil.

Methods: Subjects were all children and adolescents diagnosed with Type 1 Diabetes in the Federal University of Minas Gerais Hospital. Information collected included: gender, age and date of Type 1 diabetes diagnosis. Temporal trends were analyzed between 1980 and 2014 and divided in 5-year intervals.

Results: During this period 642 children and adolescents were diagnosed with Type 1 diabetes. From 1980 to 1994 there was an increase in the proportion of children diagnosed between 0 and 4 years old, followed by progressive decrease in the subsequent decades (47% in 1990–1994 to 20% in 2010–2014; $p = 0.01$). There was an increase in the proportion of children diagnosed between 10 and 18 years old (13% in 1990–1994 to 54% in 2010–2014; $p = 0.01$). There was no statistical difference in the proportion of children diagnosed between 5 and 9 years old through the studied time.

Conclusions: In the studied population Type 1 Diabetes in infants and toddlers seems to be decreasing throughout the years while in the age group older than 10 years, it seems to be increasing.

1. Introduction

Type 1 Diabetes is one of the most common chronic diseases in childhood and its incidence has been increasing worldwide. The Diamond study, which obtained data regarding type 1 diabetes incidence from 57 countries, between 1990 and 1999, showed an annual global increase of 2.8% [1]. Other recent studies have confirmed type 1 diabetes rapidly increase in the last two decades [2–4].

In South America, type 1 diabetes is also in the rise [5,6], although its incidence varies according to region, with lower rates in countries like Peru (0.4/100.000 per year)

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and higher rates in Brazil and Argentina (8.0/100.000 per year) [1].

Type 1 diabetes´ incidence classically varies in different age groups, with the tendency to be lower in younger children and higher in teenagers. However, a shift of the disease to younger ages has been observed since the 1990s [1]. The Eurodiab Study Group estimated that type 1 diabetes in European children younger than 5 years old would nearly double from 2005 to 2020 [7]. Temporal trend of age at diagnosis in the USA and Israel also demonstrated a higher increase of type 1 diabetes in younger children [8,9]. On the other hand, some countries like Australia, New Zeland and Japan showed a higher increase of type 1 diabetes in older groups [10–12]. Despite of its high incidence, Brazilian information about the temporal trend of age at diagnosis in the last decades is still scarce. As type 1 diabetes epidemiology varies in different regions, information about diagnosis trend in a racial miscegenated population such as Brazil´s, could be useful in the search to clarify how the interaction between genetic risk and environmental factors can influence the disease occurrence.

In this study, we investigated the temporal trend of age at type 1 diabetes diagnosis in the last four decades in a reference Pediatric Endocrinology service in the city of Belo Horizonte, Brazil.

2. Subjects, materials and Methods

This retrospective cross-sectional study was approved by the institution´s Ethical Committee.

The Pediatric Endocrinology Division of the University Hospital in Belo Horizonte (HC-UFMG) initiated its activities in 1970. Until the year 2000, it was the main public pediatric endocrinology service referral for this city and 47 others in the nearby area, covering a population estimated in 2014 of 5.829.921 inhabitants [13].

From 1977 a multidisciplinary assistance program (PAACAD) was instituted to offer a global and specialized care for the pediatric patients with diabetes, and a database with diagnosis, perinatal history, socioeconomic status and follow up information was created [14].

All children and adolescents diagnosed with diabetes who were registered in the PAACAD database were eligible for the study. This database contained patients diagnosed between 1969 and 2015.

Due to the small number of registered patients who were diagnosed between 1969 and 1979 and after 2014, our studied sample was limited to all patients diagnosed with type 1 diabetes between 1980 and 2014. Therefore, 21 patients diagnosed outside this time period were excluded from the analysis. Among these patients: 10 were diagnosed between 0 and 4 years old; 6 between 5 and 9 years old and 5 between 10 and 18 years old.

Subjects included in our study were diagnosed according the American Diabetes Association criteria [15], and had been in regular follow-up at the Pediatric Endocrinology Service of the University Hospital, under daily insulin injections.

Patients who had other types of diabetes such as Type 2 Diabetes, Monogenic Diabetes, drug-induced Diabetes or Gestational Diabetes were excluded from this study.

Data including gender, age and date of type 1 diabetes diagnosis were collected using a standardized questionnaire through the patients´ medical charts and the PAACAD database.

Temporal trends were analyzed in seven groups of 5-year intervals between 1980 and 2014: 1980–1984, 1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2009 and 2010–2014. In accordance with the WHO cut points used in the Diamond study, age at diagnosis was categorized in three groups: 0–4 years, 5–9 years and 10 years or older.

For the statistical analysis, we used the *Statistical Package for the Social Sciences* (SPSS) software version 18.0. A p value < 0.05 was considered as statistically significant. The temporal trend was analyzed using the linear trend test. We also compared the median of age at diagnosis of each quinquennial using the Jonckherrere-Terpstra test. For this analysis a p value < 0.008 was considered significant.

3. Results

The final sample included 642 type 1 diabetes patients, 339 female (52.80%) diagnosed between 1980 and 2014. The distribution according to age is displayed in Table 1. The youngest patient diagnosed was 4 months old and the eldest 18 years old. The mean age of diagnosis was 6.82 ± 3.97 and the median was 7.0 (4.0–10.0) years old. The mean age in girls was 7.09 ± 3.76 (median = 7.00) while the mean age in boys was 6.50 ± 4.18 (median = 6.0).

The temporal trend results are presented on Fig. 1. There was a significant difference in the distribution of the age groups in the quinquennials ($p = 0.01$) with a peak of the 0–4 year old group proportion in the 1990–1994 quinquennial (Table 2). A progressive decrease after this period was observed until it becomes the less frequent age group between 2010 and 2014 ($p = 0.01$). On the other hand, the 10–18 year old group, which was the less frequent in the 1990–1994 quinquennial becomes the most frequent group in the 2010–2014 quinquennial ($p = 0.01$).

The mean, median, minimal and maximal age at type 1 diabetes diagnosis in each quinquennial are shown in Table 3.

From 1980 until 1994, there was a decrease of the mean and median age at type 1 diabetes diagnosis. After 1994, the quinquennials showed an increase in mean and median age until 2014. By using the Jonckheere-Terpstra test the median age in each of these quinquennials showed statistical difference between them ($p = 0.002$). An increase of the median age since 1990–1994 was demonstrated through the Bonferroni correction showing a statistical difference between 1990 and 1994 and 2000–2004 ($p = 0.002$); 2005–2009 ($p = 0.004$) and 2010–2014 ($p < 0.001$). The temporal trend of

Table 1 – Distribution of 642 DM1 patients in an University Hospital in Belo Horizonte, Brazil, according to age.

	0–4 yo	5–9 yo	10–18 yo
n	213	251	178
%	33.17	39.09	27.72

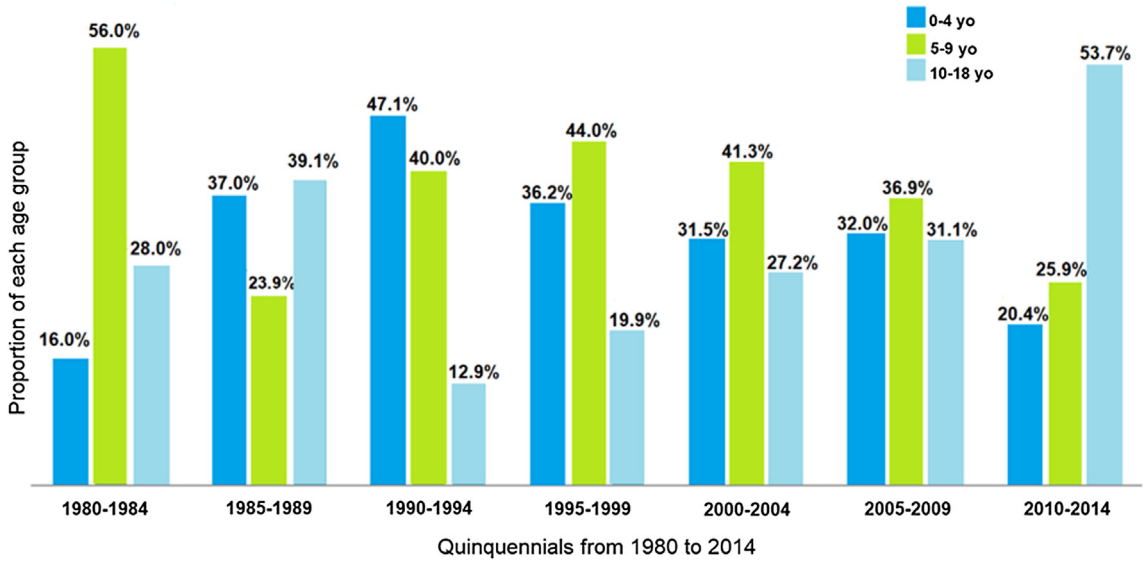

Fig. 1 – Temporal trend of age at DM1 diagnosis in 642 patients from an University Hospital in Belo Horizonte, Brazil, between 1980 and 2014.

Table 2 – Temporal trend of age at DM1 diagnosis in 642 patients in an University Hospital in Belo Horizonte, Brazil, between 1980 and 2014.

		Age at diagnosis			Total
		0–4 yo	5–9 yo	≥10 yo	
Year of diagnosis (quinquennial)	1980–1984	4 16%	14 56%	7 28%	25
	1985–1989	17 37%	11 24%	18 39%	46
	1990–1994	33* 47%	28 40%	9 13%	70
	1995–1999	51 36%	62 44%	28 20%	141
	2000–2004	58 31.5%	76 41.5%	50 27%	184
	2005–2009	39 32%	45 37%	38 31%	122
	2010–2014	11 20%	14 26%	29* 54%	54
	Total	213	250	179	642

* Significant association by the adjusted residual (p = 0.01).

Table 3 – Distribution of age at diagnosis of 642 DM1 patients in an University Hospital in Belo Horizonte, Brazil, in the quinquennials between 1980 and 2014.

	Mean	SD	Median	Minimal	Maximal
1980–1984	7.96	3.12	8.0	0	12
1985–1989	6.98	4.26	6.5	1	14
1990–1994	5.41	3.82	5.0	0	17
1995–1999	6.19	3.76	6.0	0	15
2000–2004	6.95	3.87	7.0	0	16
2005–2009	7.08	4.11	7.0	0	18
2010–2014	8.63	4.04	10	0	14

age at diagnosis presenting an U-shape curve is shown on Fig. 2.

4. Discussion

Since the 80´s, international standardized registries for type 1 diabetes incidence in children and adolescents have been showing increasing rates of the disease all over the world [16]. Although countries with the highest incidences, like Sweden [17], Ireland [18], Norway [19], and Finland [20], have shown stable rates in the last decade, it seems type 1 diabetes in children continues to rise in Brazil and in other countries [3–5].

An additional phenomenon in type 1 diabetes epidemiology that was first reported by the Diamond Study was the increment of the number of children under 5 years old who developed the disease [1]. This trend was confirmed by other studies in the following decade and higher incidence increase

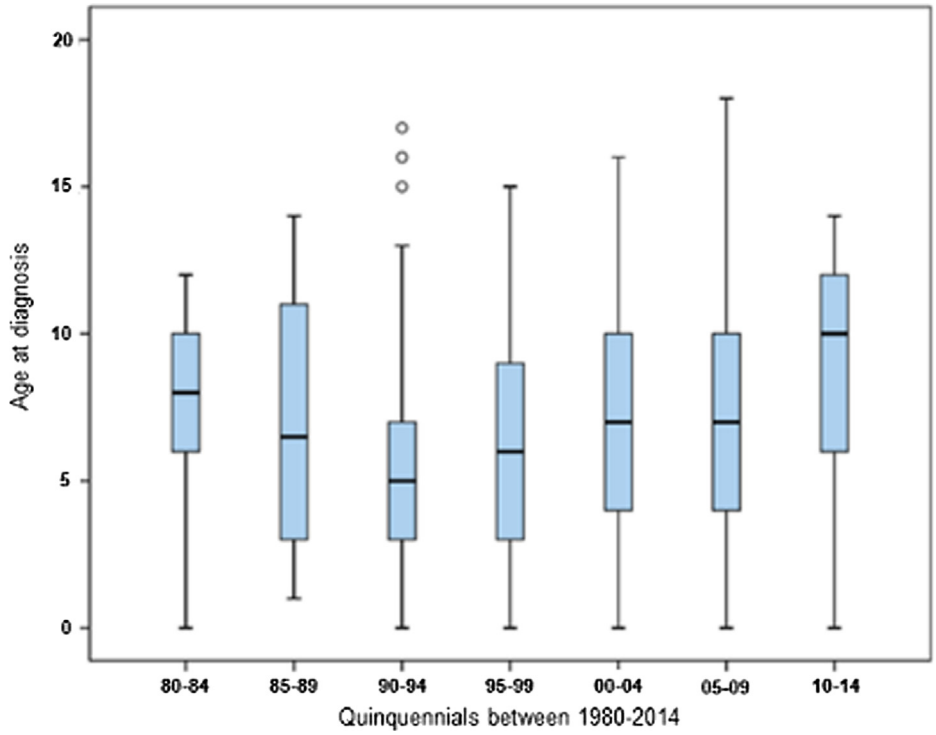

Fig. 2 – Distribution of age at diagnosis (mean ± SD) of 642 DM1 patients under 14 years old from an University Hospital in Belo Horizonte, Brazil, between 1980 and 2014.

in children between 0 and 4 year old was also observed in countries like Israel, Korea and China [9,21,22]. The latest report from the Eurodiab group, which comprised data from 1989 until 2013, confirmed a higher increase of type 1 diabetes in younger children compared to older ones [4].

In our study, the rise of type 1 diabetes in younger children that was seen in the 90 s, correspond to what was shown in the Diamond study, which analyzed trends of type 1 diabetes incidence in the same period. However, by the turn of the century, this increase of type 1 diabetes in the youngsters did not continue in our population and a shift to older children occurred in the following decades.

In fact, between 1985 and 1994, the number of patients diagnosed before 5 years of age was the highest among the three groups; on the contrary, the ones diagnosed after 10 years old became the most frequent in the 2010–2014 quinquennial.

By comparing the medians of age at diagnosis of each quinquennial, the observed tendency was the same, with the median age decreasing from 1980 to 1984 until it reaches a nadir in 1990–1994 and then rising gradually until 2010–2014.

In the United States, previous data showed an increased incidence in younger age groups, especially in the 0–4 year old. In the city of Philadelphia, Lipman et al observed a significant 70% increase in incidence among children aged 0–4 years during 2000 and 2004 compared to the previous cohorts between 1985 and 1999 ($p = 0.016$) [8]. Vehik et al, comparing registries from 1978 to 1988 and 2002–2004 in the state of Colorado found that the 0- to 4-year age-group had the largest annual increase (3.5% [95% CI 2.1–4.9] per year) compared to other age groups [23]. However, more recent data from the SEARCH for Diabetes in Youth study, which analyzed type 1 diabetes incidence in five US study centers between 2002 and 2012, showed a decrease in incidence in the 0–4 year old group during this time period. After adjustment for age, sex, and race or ethnic group, significant increases in trends were identified in all age groups except the group of participants who were under 5 years of age [3].

Despite being in Europe, Netherland´s data about type 1 diabetes incidence showed a different trend from the EURODIAB with a higher incidence in the 10–14 year old group in the last decade. Interestingly, at the start of their study (1999), the 0–4 year old group had the lowest incidence of type 1 diabetes with 7.5% (CI, 2.0–13.0) per 100 000 per year. From 1999 until 2007, the incidence in this age group significantly increased with an annual percent change (APC) of 9.2% (95% CI, 0.3–18.9), while after 2007 it decreased with a non-significant APC of −20.5% (95%CI −38.2 to 2.4). For the whole study period, a non-significant average APC of −1.8% (95% CI, −9.9 to 7.1) was observed in this age category [24].

Showing one of the highest type 1 diabetes incidence in the world, Finland also reported a higher increase rate in type 1 diabetes incidence in the 0–4 year old group between 1980 and 2005 [25]. However, in its latest publication with data between 2006 and 2011, Harjutsalo et al, reported a decline in incidence in the 0–4 and the 5–9 year age groups (57.3 to 52.8 and 80.6 to 73.0 per 100 000 person-years respectively),

and a rise in the 10- to 14-year age group (58.1 to 68.6 per 100 000 person-years) [20].

This U-shaped temporal trend in the last three decades showed in our study resembles what seems to be happening in the US, Netherlands and Finland. Such a rapid change over a short period of time could not be solely explained by shifts in genetic susceptibility and suggests that an environmental pressure might play an important role in this occurrence. The gut microbiome has being largely studied and could be a contributing factor as altered balance of the gut microbiota is reported in children with islet autoimmunity and Type 1 Diabetes [26]. Different patterns of gut colonization according to geographical location were seen in children with the same high risk HLA class II genotype [27]. Such microbiome differences in individuals with the same genotype could influence the disease manifestation and may explain how rapid changes in modern lifestyle could directly affect Type 1 Diabetes´ incidence. Epigenetic modifications might also play a role in faster epidemiological variations as the DNA methylation is partly determined by many environmental factors implicated in T1D like dietary components, antibiotics and environmental pollutants [26].

Data regarding type 1 diabetes epidemiology in Brazil is still scarce. By the end of the last century, a few study centers provided local information about incidence and prevalence of type 1 diabetes [28–31], and after the year 2000 only one city reported data about the disease [5]. In a population study in the city of Bauru, state of São Paulo, the annual incidence of type 1 diabetes in children between 0 and 14 years old, had a 9.6 fold increase from 1987 (2.82/100.000) to 2003 (27.2/100.000) [5]. More recent data from the same study group showed that between 1986 and 2015 the highest increase in incidence was in the 10–14 year old group (4.0% [95%CI: 3.2–4.8]) and the lowest in the 0–4 year old group (1.7% [95%CI: 0.6–2.7]) [32]. These findings partially corroborates what was found in our population in the last decade and could mean a tendency of type 1 diabetes incidence in the Brazilian Southeast region.

Our numbers differ from other Brazilian studies. The mean age at diagnosis we found in our group (6.82 years) was lower than the ones found in other Brazilian cities as Bauru (8.9 years) [32] and Passo Fundo (11.3 years) [28].

On the whole, we also observed a higher proportion of children diagnosed with type 1 diabetes before 5 years old (33.17%) which was close to the proportion of children who presented the disease between 5 and 9 years old (39.9%) and higher than the number of patients between 10 and 18 years old (27.72%). This finding is different from what has been usually reported in epidemiological studies with type 1 diabetes being more frequent in children older than 10 years [1].

These sort of epidemiological differences among Brazilian regions were seen before. In the 1990s, while southern cities like Passo Fundo (12/100.000) [28], Londrina (12.7/100.000) [29] and the state of São Paulo (7.6/100.000) [30], showed intermediary to high incidence rates of type 1 diabetes in children, the northeast city of Campina Grande presented a much lower number (1.8/100.000) [31]. As type 1 diabetes seems to follow an ethnic and racial distribution, which demonstrate a different degree of genetic susceptibility, and Brazil is a country of continental proportion with a variety of multiethnic compositions on its population, such epidemiological differences among regions should be expected.

A limitation of the present study is that the sample data were inadequate to estimate the true numbers of type 1 diabetes in children in the whole city of Belo Horizonte. It should be noticed otherwise that the Pediatric Endocrinology Division of the HC-UFMG is the main regional public reference center for specialized care of children with type 1 diabetes in the area, which confers strength to the findings. Despite of the establishment of smaller specialized center for the care of type 1 diabetes after the year 2000, there were no changes in the referral or accessibility for new patients in our service, that could suggest a change in the representativeness of our sample. An overall reduction of the number of patients that was seen after 2010 could be justified by the presence of other type 1 diabetes specialized centers, but also because of the progressive changes in Brazil´s demographic distribution. According to the Brazilian census, the proportion of children between 0 and 14 years old in the state of Minas Gerais, went from 33.89% in 1991 to 22.57% in 2010, a phenomenon resulting from the country´s lower fertility rate. [33] The proportion of people between 15 and 19 years old also reduced from 10.5% in the year 2000 to 8.7% in 2010[34]. Although there was a reduction of the proportion of children and teenagers, the age structure between 0 and 19 years old remained stable in the last decades [33,34].

We concluded the diagnosis of type 1 diabetes in infants and toddlers seems to be decreasing throughout the years while in the age group older than 10 years it seems to be increasing in the studied population. As the same tendency has been reported by other groups, albeit not all of them, it is intriguing to verify the reasons of these new findings.

Declaration of interests

None.

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