

Research

## Very High Incidence of Type 1 Diabetes Among Children Aged Under 15 Years in Tlemcen, Northwest Algeria (2015-2018)

### Khater S et al. Incidence of Childhood Type 1 Diabetes in Tlemcen

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#### What is already known on this topic?

- Algeria ranks among the top 10 countries with a very high incidence of type 1 diabetes in 2019.
- This study is the first to report the incidence of type 1 diabetes in children under 15 years in the region of Tlemcen in Northwest Algeria.

#### What this study adds?

- The incidence of type 1 diabetes in children under 15 years was 38.5/100 000 during 2015-2018 in the region of Tlemcen.

#### Abstract

**Objective:** In Algeria, there a lack of data of childhood type 1 diabetes (T1D). According to the estimates of the IDF 2019, Algeria ranks 7<sup>th</sup> among countries with the highest prevalence of T1D. This study aims to determine the incidence of T1D in children under the age of 15 years, living in Tlemcen in Northwest Algeria.

**Methods:** A retrospective study conducted on data of children (<15 years) newly diagnosed with T1D in Tlemcen between 2015 and 2018. The completeness of the ascertainment was measured using the two-source capture–recapture method. Total average incidences, by sex, by onset age group, and by season of onset were calculated per 100000 and per year.

**Results:** During the study period, 437 new cases of T1D were registered, among them, 233 boys and 204 girls, with a sex ratio of 1.14. The average annual incidence rate of childhood T1D was 38.5/100000 persons confidence interval (CI) (95% CI, 35.20-41.79) (boys: 40.51, 95% CI, 38.16-42.85; girls: 36.49, 95% CI, 34.17-38.80). The incidence rates in 2015, 2016, 2017 and 2018 were respectively 36.6 (95% CI, 33.72-39.48), 38.7 (95% CI, 35.43-41.97), 39.3 (95% CI, 35.97-42.62) and 39.5 (95% CI, 36.12-42.87)/100000. The most cases of newly diagnosed children were noticed in the in winter and autumn seasons. Ketoacidosis at diagnosis was present in 29.2% of patients.

**Conclusion:** The incidence of childhood T1D in Tlemcen was 38.5/100000, this incidence is in the "extremely high" category of the WHO DiaMond project classification of diabetes giving this region a very high risk.

**Keywords:** type 1 diabetes; children; incidence; Tlemcen; Northwest Algeria.

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#### Introduction

Type 1 diabetes or insulin-dependent diabetes is the most common endocrine and metabolic disorder in children, it represents 80% to 90% of diabetes in children and adolescents (1-2). Since 1950, the incidence of diabetes in children has increased substantially around the world, the World Health Organization's Diabetes Mondial (WHO DiaMond) project giving estimates of an average annual increase at around 3% (3).

The incidence of T1D varies widely across countries, and there is a geographical disparity in the epidemiological trends of childhood diabetes worldwide (4). The highest incidence rates were recorded in Finland, in Sweden and in Sardinia with, while East Asian and American Indians populations have the lowest rates (5). This geographic heterogeneity in incidence trends is due to factors such as variability in genetic predisposition and environmental factors for autoimmune destruction of beta-pancreatic cells (6-7). The role of environmental triggers in the development of childhood diabetes has been suggested because of the marked seasonal variation in the onset of childhood diabetes (8).

According to the 8<sup>th</sup> edition of the International Diabetes Federation (IDF) Diabetes Atlas estimates, Algeria ranks in seventh position worldwide among countries with the highest estimated number of prevalent children aged under 15 year with T1D (20 100) (9), and the first country in the MENA (Middle East and North Africa) Region with the highest number of new cases (incidence) of T1D in this age group with 3100 children in 2019 (10).

In Algeria there is a lack of available scientific data on the incidence and prevalence of T1D in children, with only three functional regional registries for T1D in children under 15 years of age (11). In Algiers (in north-central of Algeria), the

incidence of T1D among children under 15 rose from 22.3 per 100 000 in 2010 to 29.0 per 100 000 in 2015 (12). In Oran (northwest region of Algeria), the incidence of T1D in children under 15 rose from 4.7 per 100 000 in the period 1979-1988 to 24.46 per 100 000 in the period 2010-2014 with an annual increase of incidence of 5.04 (13-14). As for Constantine (northeastern region of Algeria), the incidence of T1D in children under 15 increased by 9.57 per 100 000 between 1990-1994 to 17.44 per 100 000 in 2003 (15). However, in the region of Tlemcen in the North-West of Algeria, no epidemiological data on T1D in children are available.

The objective of this study is to assess the incidence of T1D in children under 15 years from the region of Tlemcen, in northwestern Algeria between January 1<sup>st</sup>, 2015 and December 31, 2018.

## **Patients and Methods**

### **Study design and data collection**

This retrospective study was conducted in Tlemcen, one of the largest cities in northwestern Algeria. This region bordering on Morocco is defined by a diverse geography, a Mediterranean climate and Arab Muslim sociodemographic structure. According to the 2014 census, the population numbers 1,032,065 inhabitants and the population of children under 15 years is estimated at 267,597 children (male: 136,084; female: 131,513), accounting for 25.93% of the total population. There are five pediatric units in Tlemcen: pediatric department of the Mother and Child Specialized Hospital at Tlemcen's Teaching Hospital, and pediatric departments of four Public Hospitals (PH), PH of Maghnia, PH of Ghazaouet, PH of Remchi and PH of Sebdu.

The mid-year estimates of the children population under 15 years were provided from the annual statistical census data of the office of Ministry of the Interior and from the regional Statistical Office of Tlemcen.

The diagnosis of T1D was made by the pediatric physician, according to the accepted criteria of the American Diabetes Association (16). The date of diagnosis of diabetes was accepted as the day of the first insulin injection. The months of diagnosis of T1D were sorted by seasons to examine the possibility of seasonality in the onset of childhood diabetes. The presence of ketoacidosis at the time of diagnosis were recorded. According to the recommendations approved by the ISPAD Clinical Practice Consensus Guidelines (17), diabetic ketoacidosis (DKA) was defined as pH <7.30 and /or serum bicarbonate < 15 mmol/L.

We included in the study all children under 15 years of age living in in the region of Tlemcen for at least 6 months prior to diagnosis, and presenting a newly diagnosed T1D for the period from January 1<sup>st</sup>, 2015 to December 31, 2018. We excluded children with another type of diabetes (type 2 diabetes mellitus, neonatal diabetes, maturity onset diabetes of the young, and diabetes caused by other conditions).

The main source data on children diagnosed with T1D were based on the registers and the hospital records of the pediatric department of the Mother and Child Specialized Hospital at Tlemcen's Teaching Hospital, and derived from the hospital records of pediatric departments of the four Public Hospitals at Tlemcen. In the region of Tlemcen, all children under the age of 15 years, newly diagnosed with T1D are referred to these pediatric units of these five public hospitals, as they are the only ones authorized to write a report for the initiation of insulin treatment and for follow-up.

The secondary independent data source of ascertainment was based on the Algerian social security system (Algerian national health insurance ANHA). In Algeria, every child with T1D receives free treatment, in fact diabetes is one of the chronic conditions which benefit from full coverage by the Algerian State (ANHA)

To measure case ascertainment and confirm the completeness of the recording we have used the capture-recapture method (18). This method would be expected to identify all new cases of children with T1D by capturing them in the first source and recapturing them in the second source in order to minimize the probability of underestimating of the real number of new cases and to adjust accordingly the incidence of childhood T1D in the region.

We consider that we have carried out the census of all children under 15 years newly diagnosed with type 1 diabetes during this period of study in the region of Tlemcen.

This study was approved by the University Ethics and Deontology Council of the University of Tlemcen, Tlemcen, Algeria (approval number: N° CEDUT/DZ/019/117), informed consent was obtained from the parents of children.

### **Statistical Analysis**

The average annual incidence rates were calculated by dividing the newly diagnosed cases of T1D in children aged under 15 years in a specific year, by population at risk aged under 15 years residing in Tlemcen in that year, and is expressed per 100 000 persons per year. Total average incidences were calculated by sex, by the three pediatric age group (0-4, 5-9 and 10-14 years) and by the season of the year at diagnosis.

The 95% confidence intervals (CI) of the annual incidence rates were calculated based on Poisson distribution. Independent Chi squared test was used to compare the rates between years, sexes and age groups, a p-value ( $p$ ) <0.05 was considered significant. Poisson regressions were used to analyze the changes in diabetes incidences with age, sex, season at diagnosis and year period. Statistical analysis was performed using the software R (x64 3.3.2).

### **Results**

Overall ascertainment with capture-recapture method using the two independent sources was estimated to be 96% complete for the study period.

During the period from 1<sup>st</sup> January 2015 to December 31, 2018, 437 new cases of T1D in children under 15 were registered in the region of Tlemcen, among them 233 (53.32%) boys and 204 (46.68%) girls, with a male/female sex ratio of 1.14.

When children were classified into three age groups, 29.06% of children were diagnosed under the age of 5 years, 34.78% and 36.16% of children were diagnosed in the 5-9 years and 10-14 age groups respectively (Figure 1).

The mean age at onset of T1D in this population was 7.51±4.12 years (95% CI, 6.56-8.35), with no significant difference between boys 7.46±4.14 years (95% CI, 6.40-8.62) and girls 7.56±4.11 years (95% IC, 6.70- 8.21) ( $p>0.05$ ).

The average annual incidence rate of T1D among children in these 4 years was 38.5 new cases per 100 000 per persons under 15 years old (95% CI, 35.20-41.79) (boys: 40.51, 95% CI, 38.16- 42.85, girls: 36.49, 95% CI, 34.17-38.80), The difference in the incidence rate between boys and girls was only statistically significantly different in 2015 ( $P=0.00064$ ), for the other

years of study, there was no significant preferential difference between boys and girls ( $p > 0.05$ ). The incidence rates in 2015, 2016, 2017 and 2018 were respectively 36.6 (95% CI, 33.72-39.48), 38.7 (95% CI, 35.43-41.97), 39.3 (95% CI, 35.97-42.62) and 39.5 (95% CI, 36.12-42.87) per 100 000 respectively without significant difference between these 4 years of study. The number of cases and annual incidence rates by sex are presented in Table 1.

The incidence of T1D was lower in children of 0-4 years old years (31.11 per 100 000, 95% CI, 29.12-33.09) and higher in the 5-9 and 10-14 years age groups, with a peak of 44.78 per 100 000, 95% CI, 42.96-46.59) between 5-9 years, these differences between age groups of onset of childhood diabetes were not statistically significant ( $p > 0.05$ ). The annual incidence rates by sex and by age groups are presented in Table 2 and Table 3.

Poisson regression results show that the 5-9 years old group had 1.43 times risk, and the 10-14 years old group had 1.31 times risk than 0-4 years old group ( $p < 0.05$ ). During this 4-year study period, there was no significant increase in the overall annual incidence of T1D.

The study of the seasonality in the diagnosis of T1D has shown that the most cases in the region of Tlemcen occurred in autumn (25.06%) and winter (28.25%), the cooler and rainier seasons of the year but less in spring and summer (24.45% and 22.24%, respectively), the warmer seasons of the year, but the seasonal variation were not statistically significant ( $p > 0.05$ ). This onset seasonality has been identified in both sexes and in the three age classes. November was the month with the highest number of newly diagnosed children (9.83%) and June was the month with the lowest number of new cases (5.72%). A total of 138 children (29.2%) had ketoacidosis at the diagnosis of T1D. DKA was more common (53.62%, 74/138) among females, without significant difference between boys and girls ( $p > 0.05$ ). Regarding the frequency of DKA by age groups we observed that children aged  $< 5$  years had higher (38.86%) DKA frequency than the 5 to 9 (32.71%) and 10 to 14 year-old children (27.43%), although the difference was not statistically significant ( $p > 0.05$ ).

### Discussion

This study is the first to produce reliable estimate of the incidence of T1D in children under 15 years in Tlemcen. During this 4-year period of study, the incidence of T1D in children was estimated at 38.5 per 100 000 children under 15 years per year. Our results show that the region of Tlemcen presents a very high risk of T1D in children under 15 years.

In Algeria there are only some reports on the epidemiological profile of T1D in children aged under 15 years. Nevertheless, the incidence in our child population is comparable to that of other studies conducted in Algeria. Recently in 2016, in the capital Algiers, the incidence of T1D was 29.35 per 100 000 children under 15 years (19). In the region of Oran, the incidence of T1D in children under 15 was 31,12 per 100 000 in the period 2013-2017 (20). In all the data from these studies in Algeria, T1D incidence in children is in the "extremely high category" (incidence rate  $\geq 20$  per 100 000 persons per year) of the WHO DiaMond project classification for diabetes (21).

There is a clear difference in the incidence of childhood T1D in these different regions of Algeria, similar differences in the incidences of T1D in children between regions of the same country are well documented (21-22-23).

During this study period, the incidence of childhood T1D ranged from 36.60 per 100 000 in 2015 to 39.50 per 100 000 in 2018, but due to the short period of our study, we cannot estimate the rate of increase in the incidence of T1D in children under 15 years old in the region.

Worldwide, after the Nordic countries (Finland, Sweden, and Norway), some countries with an Arab population (Kuwait and Saudi Arabia) have the highest rates of T1D (9). In Africa, epidemiological data are incomplete and many countries have no studies on the incidence of T1D in children. The incidence of childhood diabetes in Tlemcen is clearly higher than in neighboring countries, notably Tunisia (7.7 per 100 000) during 1990- 1999 (3), Libya (7.8 per 100 000) during 1991-2000 (24), Sudan (10.1 per 100 000) in 1990 (25), Egypt (3.1 per 100 000) in 2011 (26). It is also higher than in some MENA countries, notably in Qatar (31.83 per 100 000) in 2016 (27), in Iraq (8.0 per 100 000) in 2016 (28) and in Turkey (10.8 per 100 000) during 2011-2013 (23), but it was lower than that of eastern Saudi Arabia (52.93 per 100 000) in 2007 (29) and then that of Kuwait (40.9 per 100 000) during 2011-2013 (30). It should be noted that the studies carried out in most of the north African countries mentioned are older. This highly rate of incidence of T1D in our population in Tlemcen compared to neighboring countries is presumably due to as yet undetermined genetic or environmental factors.

In comparison with the Mediterranean countries, the incidence of diabetes in our pediatric population is higher that of Spain (22.84 per 100 000) during 2013-2016 (31), France (19.1 per 100 000) in 2015 (32), Italy (25.2 per 100 000) during 2009-2013 (33), Montenegro (18.8 per 100 000) in 2011 (34), Croatia (17.23 par 100 000) during 2004-2012 (35), and Cyprus 11.4/100000 during 2011-2016 (36) but it remains lower than that Sardinia (51.0 per 100 000) during 2007-2009 (37).

In our study, the mean age of diagnosis of type diabetes was 7.51, which was high compared to Saudi Arabia (7.0 years) (38), but lower than those of Kuwait, Spain and Turkey (respectively 8.1, 8.3, and 9.1 years) (30-31-39). In this study also, approximately one-third of children were diagnosed below 5 years of age which lowered the average age of diagnosis of type diabetes in our pediatric population to 7.51 years, recent data in several regions of the world have also shown a large increase in the incidence of T1D in the youngest age-group (0-4) years (3-40). It is well known that the incidence of childhood diabetes differs by age groups and peaks at pubertal period. Moreover, an increase in the incidence of diabetes with age to puberty has been reported in several regions in the world (3). In this period of study, the highest incidence rates in this region were observed in the age groups of 5-9 years and 10-14 years. In this children population, the incidence increases with age and peaking between 5-9 years, which is similar to studies conducted in Kuwait (30), in Italy (33), and in Finland (41). While Saudi Arabia (38), Turkey (23), Spain (31), Croatia (35) and some regions of Algeria (12-14-15), have described peak incidence of T1D in the 10 to 14 age group.

The incidence of childhood diabetes may differ by gender, in our population of Tlemcen, the number of incident cases of T1D is slightly higher in boys than in girls, but the incidence rates were only statistically different in 1 year (in 2015) between boys and girls. However, no significant difference in the incidence of childhood diabetes between boys and girls has been observed in Algiers (19) and in several countries of the world (30-31-33-41). In contrast, a female predominance is observed in Saudi Arabia (38), and a male excess has been observed in Hungary (42) and in Finland (43).

The seasonality of the onset of childhood diabetes has been confirmed by the Eurodiab study, and the existence of a winter peak in the onset of childhood diabetes has been described in different regions of Europe (44). During this 4-year period, we

noted a predominance of winter peak without significant seasonal variation in the onset of T1D in the region of Tlemcen. Similar findings were reported in other regions of Algeria (12-20) and in other countries (26-27), where more cases of childhood T1D occurs in the winter season. In opposition, higher incidences were observed in the spring season in Diyarbakir in the Southeast region of Turkey (39). This seasonal variation consolidates the hypothesis of a viral origin triggering childhood diabetes (8), principally the hypothesis of the infection by enterovirus (45).

Worldwide, the DKA frequency at diagnosis of T1D varied from 12.8% to 80% (46). However, the frequency of DKA as first manifestation of T1D during this study period was 29.2%, and recently in 2016 in the capital Algiers, 17.6% of children aged 0–14 years presented with DKA (19). Compared to the previous studies in other countries, the frequency of DKA in our diabetic children was higher than in Spain (17.8%) (47) and in France (14.8%) (48), but was lower than that reported in Kuwait (33.6%) (49), in Saudi Arabia (40%) (29) and in Turkey (65.9%) (39).

#### **Study Limitation**

However, this study presented some limitations. First, it was possible that some cases of monogenic diabetes in children was misclassified because genetic testing for monogenic causes were not routinely practiced in all new children diagnosed with diabetes before 9 months. Second, due to the short duration of the study we cannot describe trends of childhood diabetes in this region. Third, we cannot explain the causes of the very high incidence of childhood diabetes in our population because the data on genetic susceptibility factors and environmental triggers are limited.

#### **Conclusion**

The incidence of childhood T1D in Tlemcen in Northwest Algeria was 38.5 per 100 000, this incidence is in the "extremely high" category of the WHO project classification for diabetes giving the region a very high risk. Other large-scale epidemiological studies at the national level should be conducted to determine the incidence of childhood diabetes mellitus in Algeria and further studies on genetic and environmental risk factors for T1D are needed to better explain the high incidence of T1D in children in Algeria.

**Conflict of interest:** The authors declare that they have no conflict of interest.

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#### **Authorship Contributions**

**S.K:** Literature research; Definition of intellectual; content Acquisition of data, Data analysis; Statistical analysis; Manuscript preparation; Manuscript editing; Manuscript review.

**A.A and SB:** conception and design of the manuscript, Manuscript editing and manuscript review.

**N.C:** Manuscript editing; Manuscript review.

**N.B and A.M:** Data analysis; Statistical analysis.

**H.H and Z.M:** Acquisition of data; Literature search.

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**Table 1.** Number of cases and annual incidence of Type 1 diabetes among children under 15 years age per 100000 persons per year (95% CI) by sex in Tlemcen between 2015 and 2018

Year	Total		Boys		Girls	
	Number of cases	Incidence rate (CI)	Number of cases	Incidence rate (CI)	Number of cases	Incidence rate (CI)
2015	99	36.60 (33.72-39.48)	62	45.02 (42.71-47.32)	37	27.80 (25.53-30.06)
2016	108	38.70 (35.43-41.97)	58	40.89 (38.55-43.22)	50	36.47 (34.17-38.76)
2017	113	39.30 (35.97-42.62)	53	36.28 (33.90-38.65)	60	42.49 (40.15-44.82)
2018	117	39.50 (36.12-42.87)	60	39.87 (37.46-42.27)	57	39.19 (36.82-41.55)
2015-2018	437	38.50 (35.20-41.79)	233	40.51 (38.16-42.85)	204	36.49 (34.17-38.80)

CI: confidence interval

**Table 2.** Annual incidence of Type 1 diabetes among children under 15 years age per 100000 persons per year (95% CI) by age groups in Tlemcen between 2015 and 2018

Year	Age group (years)		
	0-4	5-9	10-14
2015	41.91 (39.93-43.88)	34.45 (32.66-36.23)	32.71 (30.82-34.59)
2016	23.82 (21.85-25.78)	64.50 (62.7-66.29)	31.76 (29.83-33.68)
2017	25.05 (23.05-27.04)	46.39 (44.55-48.22)	48.31 (46.36-50.25)
2018	33.68 (31.65-35.7)	33.78 (31.93-35.62)	50.89 (48.92-52.85)
2015-2018	31.11 (29.12-33.09)	44.78 (42.96-46.59)	40.92 (38.97-42.86)

**Table 3.** Annual incidence of Type 1 diabetes among children under 15 years age per 100000 persons per year (95% CI) by sex and by age groups in Tlemcen between 2015 and 2018

year	Boys			Girls		
	Age group (years)			Age group (years)		
	0-4	5-9	10-14	0-4	5-9	10-14
2015	54.37(52.97-55.76)	43.35 (41.92-44.77)	36.53 (35.18-37.87)	29.06 (27.69-30.42)	25.15 (23.9-26.39)	27.94 (26.6-29.27)
2016	21.51 (20.09-22.92)	67.81 (66.52-69.09)	37.55 (36.18-38.91)	26.20 (24.81-27.58)	61.05 (59.79-62.3)	25.79 (24.45-27.09)
2017	20.27 (18.81-21.72)	34.05 (32.74-35.35)	54.69 (53.3-56.06)	29.35 (27.95-30.75)	59.27 (57.99-60.54)	41.74 (40.37-43.07)
2018	33.17 (31.71-34.62)	39.67 (36.85-42.48)	47.19 (45.79-48.59)	34.20 (32.77-35.62)	27.62 (26.32-28.91)	54.70 (53.31-56.08)
2015-2018	32.33 (30.9-33.75)	46.22 (44.93-47.5)	43.99 (42.61-45.72)	29.70 (28.36-31.03)	43.27 (42.0-44.53)	37.54 (36.17-38.9)

**Figure 1:** Number of new cases (males and females) of T1D by age groups in the 2015–2018 period.



Uncorrected proof