Cytogenetic Profile and Main Comorbidities of School-Aged Children and Adolescents with Down Syndrome in the Northwestern Algeria

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Abstract

Down Syndrome (DS) is the most common chromosomal aberration in humans, associated with several conditions. The aim of our study is to describe the main comorbidities associated with DS at the school-age, with the cytogenetic profile and contributed risk factors.

A 7-year retrospective, descriptive study was carried out from 2010 to 2017, based on the psychoeducational centers for mental health (CPPs, UDM and ANIT) in Tlemcen. Data collected using a pre-established questionnaire for DS parents and referring to children's medical and administrative records.

Among 207 patients with DS, 36 were identified with cytogenetic study, 97.22% were free trisomy, 2.78% mosaic and no translocation's cases. The sex ratio (M:F) was 1.58 :1 and the median age was 11.7 years. The main age of DS mothers was 36.32 years. Of the 133 individual with clinical morbidities, the most common was ophthalmologic (20%), ENT (24.06%) and CHD defect (16.92%), followed by thyroid (9.23%) , gastroenterological (9.23%) and CNS disorders (9.23%). No associations were found between maternal age or parental consanguinity and risks of congenital conditions. Risk of developing CHD, Refraction disorders or also Epileptic seizures increase with age.

Children with DS have several DS-specific morbidities. Advanced maternal age is one of major risk factors for giving birth to a child with DS. The prevalence of clinical comorbidities in our population was significantly lower than others of literature, because of the younger age of sample study, and the selective nature of psychoeducational centers.

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Introduction

Down syndrome (**DS**), or trisomy 21(**T21**), is one of the major causes of congenital malformation, intellectual disability and handicap, being considered the most frequent chromosomal aberration with a general presentation from 1:700–1:1000 live births[1,2]. In Algeria, its frequency is about 80,000 cases[3].

DS is characterized by the presence of an extra chromosome 21 generally resulting from non-disjunction during maternal meiosis, and in rare instances as a part of Robertsonian or reciprocal translocation[4]. The diagnosis of newborns with DS on the basis of clinical features usually presents with no particular difficulty and it has been reported from 73% to 100%[5]. Nevertheless, even an experienced physician may find it occasionally difficult to give a confirmatory diagnosis on an infant when the clinical features may be minimal. Karyotyping is essential for confirmation of the clinical diagnosis.

With the recognition of advanced maternal age as risk factor associated with DS[6], other risk factors are less well established such as maternal parity, genetic predisposition and may be an autosomal recessive gene mutation, particularly in the Middle East where the rate of consanguinity is increasing[7].

Individuals born with Down syndrome have an increased risk for multiple malformations and

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medical conditions, including cardiovascular disease, auditory and ophthalmic disorders, infections, neurological and orthopedic conditions, and hypothyroidism and diabetes[8-15]. They also are at increased risk for cognitive impairment[13]. Most patients with DS require treatment during childhood because of mental or growth retardation.

People with DS are known to have shortened life spans. In the last century, however, their life expectancy has dramatically increased, from 9 years in 1929[16] to 60 years in 2002[17]. It was estimated that persons with DS will be living as long as the general population within a generation[18], and age-specific risk for mortality is considerably increased compared with other people with intellectual disabilities[19]. This increase has been related to significant medical advances in recent decades, such as improvements in cardiac surgery, prevention of childhood infections, broader access to standard care, and a better global psycho-social support for the DS population[20].

The present paper aims to describe the demographic and cytogenetic profile, to investigate about the main clinical characteristics of a cohort of individuals with DS from Tlemcen's Population in western Algeria, and to analyze their differences according to age, maternal age and gender groups.

Materials and methods

This is a retrospective record-based descriptive study conducted in the Laboratory of human actions' valorization for public health of Tlemcen's University, with the collaboration of the psycho-educational centers (**CPP**), and the associations of ; union of the mentally retarded (**UDR**) and national association for integration of trisomy (**ANIT**).

207 DS patients (with or without chromosomal studies), aged between 3 and 25 years old [**Table 1**], were referred over nine centers (seven CPPs and two associations) in Tlemcen, on the Northwestern Algeria, during the period from 2010 to 2017.

The clinical evaluation was carried out by physical examination (Phenotypic clinical features of DS), using a detailed protocol which is routinely used at these centers. Data recorded in the medical charts were as follows: mongoloid facies, protruding tongue, transverse single palmar crease, brachycephaly, depressed nasal bridge, small, low-set ears, and upward-slanted eyes with epicanthic fold, short neck and hypotonia.

	Number (%)
Age at referral (year)	
Minimum–maximum	3 to 25
Mean ± SD	11.69 ± 4.92
Sex (N=207)	
Male	127 (61.35%)
Female	80 (38.65%)
Sex ratio (M:F)	1.58 :1
Birth order (N=175)	
First	22 (12.57%)
Second	25 (14.29%)
Third	46 (26.29%)
Fourth and more	82 (46.85%)
Parental consanguinity (N=169)	27 (16%)
First degree	10 (6%)
Second degree	132 (78%)
None	
Maternal age (years)	19 to 50
Minimum–maximum	36.32 ± 6.16
Mean ± SD	
Family history	9 (4.35%)
DS history	6 (2.90%)
MHS history	
Maternal miscarriages (183)	10 (4.83%)
Two and more	183 (88.40%)
No miscarriages	

Table 1: Sociodemographic features of 207 referred cases of DS.
MHS: Mental Health Syndrome

Anthropometric parameters and general data were collected by using a pre-established questionnaire for parents. Data include age, sex, birth order and patient's geographic origin, age of their parents, parental consanguineous marriage, number of maternal miscarriages, and family history of DS or other mental disabilities. When an individual's origin was not from Tlemcen, he/she was excluded from the study.

Data about clinical complications were collected from patients medical records and/or information provided by their mothers with help of centers' doctors and specialized staff. When an individual was not evaluated for a specific characteristic, he/she was excluded from the frequency analysis of this characteristic.

Data about cytogenetic abnormalities were collected from 36 patients that had been partially referred to Cytogenetics laboratories, Karyotypes were identified by standard RHG banding technique.

Data were processed using R software (R version 3.2.3 (2015-12-10)). Subjects were classified into groups according to schooling age (under 8, 8--12, 13--18, and over 18 years), or presence of clinical conditions. We also performed a gender-stratified analysis in the whole sample, and according to age groups. We compared Demographic characteristics and the prevalence of different clinical comorbidities, between groups. Qualitative results are presented as percentages, whereas quantitative results are presented as mean ± standard deviation (SD). A Chi-square test was used to evaluate statistical significance in the comparison of categorical variables. Results with $p < 0.05$ were considered significant.

Results

A total of 207 patients with DS clinical features, among them, 36 (17.4%) were confirmed by cytogenetic study. The mean age at referral was 11.69 years and the sex ratio was 1.58:1. About 73.14% of the cases were of third and more birth orders, and parental consanguinity was reported in 24 % of the cases [Table 1]. The mean maternal age at the birth of DS child was 36.32 years (19-50) [Figure 2]. The abnormal karyotypes are listed in [Figure 1]. Nondisjunction was the most common type of abnormality (97.22%), followed by mosaic (2.78%) and there were no cases with translocation (0%) [Table 2]. Summarizes the main clinical conditions of DS patients in our population's study, The prevalence of subjects with clinical conditions was 62.80% (130/207). Ear–nose–throat (ENT (23.85%)), Ophthalmologic disorders (20%) and congenital heart diseases (16.92%) were the most prevalent groups of diseases in the sample's study, followed by central nervous system (CNS (9.23%)), Gastroenterological (9.23%) and Thyroid disorders (6.92%). A significant difference between age groups ($P < 0.05$) were found in four groups of medical conditions (congenital hearth diseases, ophthalmologic and central nervous system disorders and gastro-esophageal reflux disease).

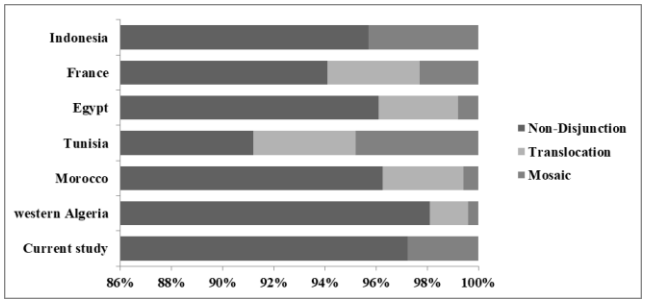

Figure 1. Comparison of the current study's cytogenetic profile with other population data worldwide[22-25, 27,28].

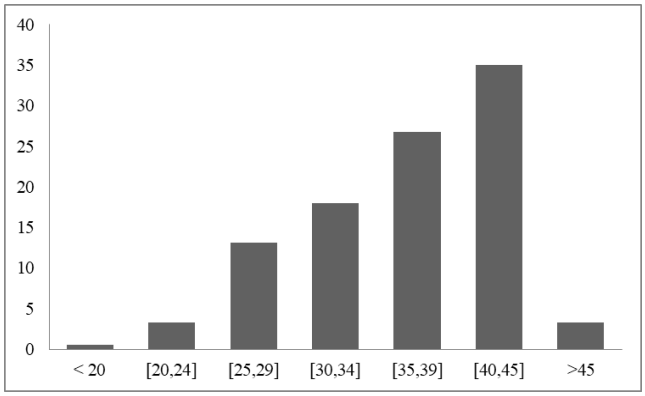

Figure 2. Mothers' ages of individuals with DS at delivery.

Discussion

In the present study we have firstly examined cytogenetic and sociodemographic characteristics, than we have represented the prevalence of medical conditions in school-aged children with DS, and compared the frequencies of these conditions in different episodic age of children with DS to identify any variation in health status over time. In addition, the study investigated whether there were any correlation between risk factors and congenital defects.

From a total of 207 people referred to the specials centers (CPPs, UDR, ANIT) during a 7-year period, 36 cases had a Karyotype analysis which represents only 17.4% of the study sample, the remains were diagnosed on the basis of clinical features. All cases were diagnosed postnatally, prenatal diagnosis of DS is not practiced in Algeria. In our country like in developing countries, the diagnosis of DS is still done in the neonatal period, and on the basis of clinical features, even the clinical diagnosis of this condition is usually done without difficulty and has been reported to range from 73% to 100%[5]. A confirmatory diagnosis on an infant

with minimal clinical features remains difficult. Karyotyping is essential for confirmation of the clinical diagnosis.

The distribution of the different karyotype patterns observed in the present study is shown in Figure 1.The percentage of free trisomy 21 was 97.22%, mosaic trisomy 2.78% and there were no cases with translocation trisomy. This data is relatively compatible with the data from international studies (Figure 1)[22-25, 27,28]. No cases with translocation trisomy may reflect the low sample study number. For the most international studies, the frequency of translocation and mosaicism was very much lower than the frequency of free trisomy 21.

The age at referral ranged from3 to 25 years, with a mean of11.69 years. This may reflect the schooling age, because of the study sample came from educational centers, and referral to these institutions is possible only at the age of schooling which is 6 years in Algeria.

The overall sex ratio was 1.58 :1. No differences were found between age groups. The excess of males appears to be universal and was reported in many studies in different regions of Algeria and from other countries[21-26].

In our study, average maternal age at birth of the DS child was 36.3 years. 65% of DS patients were born to mothers older than 35 years of age (Figure 2). These data are consistent with previous studies from Algeria and in different countries[22-25]. This clearly indicated that maternal age was a major contributing risk factor.

Parent's consanguinity was observed in 22% of the DS children. This result agrees with others[23, 26]. However, the effect of consanguinity on nondisjunction of chromosome 21 has not been clearly defined [29, 30].

In the second part we represent the prevalence of medical conditions in our population study, and compare the frequencies of these conditions in different episodic age. Few series have approached the study of clinical conditions in DS population, and our data represent the first study in Tlemcen, northern Algeria. In this paper, clinical defects were detected in more than 60% (133/207) of cases with DS. These results reconfirm that patients with DS present a high prevalence of several medical conditions[32]. Many of which are congenital others may start before the first decade of life (Table 2). Unlike in literature who reported the cardiac defects to be the most common occurring birth defect associated with Down syndrome[32, 33], our study shown that ENT diseases (24%) and ophthalmological conditions (20%) were the most prevalent defects associated with DS, followed by congenital hearth diseases (CHD (17%)), thyroid, gastroenterological and CNS disorders placed in the third order. We found a significant reduction of the prevalence of the major clinical conditions, compared to the worldwide population (Table 3)[10,12,14,15,28,31,34,37-41]. The difference may reflect low sample study number, and the schooling nature of the referral centers who could not accept children with several illness. When children are stratified by age we found that about ophthalmologic, CHD and CNS disorders were reported to be associated with increased ongoing problems in the later cohort age. Moreover, the overall reduction in first decade was reported in all of the romaine conditions. No significant differences were found in the major conditions associated to age groups. This may reflect younger age of children, because of more than 50% of clinical conditions appear at adult age of individuals with DS[26].

In Table 4, we investigated about association between Maternal age, parental consanguinity and having a child with clinical comorbidities. There were no association. Our data differ from those reported in literature specially for congenital complication such as CHD which largely studied, and it found that mothers over35 years old were more likely to give birth DS child with a CHD than DS children born to mothers under 35 years of age[21]. There were also no differences between gender. Those results may reflect low sample study number, or also the schooling selected nature of the referral centers.

Conclusions

This study has provided that children and adolescents with DS have several DS-specific morbidities and screening programs are absolutely necessary to support and educate patients and their families. In general terms a similar tendency was observed in the karyotype of our population study among the different reports. Moreover advanced maternal age remains the major risk factor associated with DS, without increasing the risk of congenital or clinical

morbidities. Because of medical advances and improvements in overall medical care, the median survival of individuals with DS has increased considerably, but that does not overlook the increase risk of medical defects with age. Our population study may be not representative of all Tlemcen's population with DS, the study must include newborns and children from pediatric departments, adults with DS should also be included.

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Declaration of Interest

The authors report no conflict of interest and the article is not funded or supported by any research grant.

Clinical characteristic	Total n=133 (64.25%)	Under 8 n=27 (62.79%)	8-12 n=55 (71.43%)	13-17 n=27 (50%)	Over 17 n=24 (80%)	Pearson	*P*-Valuo
ENT	32 (24.06%)	5 (18.52%)	13(23.64%)	8(29.63%)	6 (25%)	0.93	ns
SAS	23 (17.9%)	4 (14.81 %)	10 (18.18%)	6 (22.23%)	3(12.5%)	0.99	ns
Hearing loss	4 (3.08%)	0	2 (3.64%)	1(3.70%)	1(4.17%)	1.07	ns
Other ENT diseases	4 (3.08%)	1(3.70 %)	1(1.82%)	1(3.70%)	2(8.33%)	1.96	ns
Ophthalmologic	26 (20%)	4(14.81%)	6(10.91%)	8(29.63%)	8(33.33%)	7.64	0.054
Strabismus	14 (10.8%)	3(11.12 %)	4(7.27%)	4 (14.81%)	3(12.5%)	1.25	ns
Refraction disorders	12 (9.23%)	1(3.70 %)	2(3.64%)	4 (14.81%)	5(20.83%)	8.06	<0.05
CHD	22 (16.92%)	4(14.81%)	15(27.27%)	2(7.41%)	1(4.17%)	8.94	<0.05
AVSD	8 (6.15%)	1 (3.70 %)	6(10.91%)	1(3.70 %)	0	4.38	ns
VSD	4 (3.08%)	1 (3.70 %)	2(3.64%)	0	1 (4.17%)	1.07	ns
ASD	3 (2.30%)	1 (3.70 %)	2 (3.64%)	0	0	1.91	ns
Surgical correction	7 (5.38%)	1 (3.70 %)	5(9.10%)	1(3.70 %)	0	3.21	ns
CNS	12 (9.23%)	4 (14.81%)	2(3.64%)	3(11.11%)	3 (12.5%)	3.54	<0.05
Epileptic seizures	4 (3.08%)	3 (11.12 %)	0	0	1 (4.17%)	8.73	<0.05
SMR	6 (4.61%)	1 (3.70 %)	2 (3.64%)	1 (3.70 %)	2 (8.33%)	0.99	ns
Autistic behavior	1 (0.80%)	0	0	1 (3.70 %)	0	3.95	ns
Depression	1 (0.80%)	0	0	1 (3.70 %)	0	3.95	ns
Gastroenterological	12 (9.23%)	0	7 (12.73%)	1(3.70%)	4(16.67%)	6.24	ns
Celiac disease	5 (3.85%)	0	5 (9.10%)	1(3.70 %)	0	5.13	ns
Constipation	4 (3.08%)	0	2 (3.64%)	0	1 (4.17%)	2.12	ns
GERD	3 (2.30%)	0	0	0	3 (12.5%)	13.94	<0.05

Thyroid	12 (9.23%)	5 (18.52%)	4 (7.27%)	2 (7.41%)	0	6.00	ns
Hypothyroidism	5(3.85%)	2 (7.41%)	1 (1.82%)	2 (7.41%)	0	3.49	ns
Hyperthyroidism	4(3.08%)	3 (11.12 %)	3 (5.45%)	0	0	5.25	ns
Diabetes mellitus	4(3.08%)	0	3 (5.45%)	0	1(4.16%)	2.91	ns
Musculoskeletal	4(3.08%)	1(3.70%)	2 (3.64%)	1(3.70%)	0	0.91	ns
Urologic	2(1.54%)	0	1(1.82%)	0	1(4.16%)	2.01	ns
Skin	2(1.54%)	1(3.70%)	0	1(3.70%)	0	2.97	ns
Asthma	1(0.80%)	0	1 (1.82%)	0	0	1.43	ns
Other complications	4(3.08%)	2 (7.41%)	1(1.82%)	1(3.70%)	0	2.85	ns

Table 2. Main clinical comorbidities of children and adolescents with DS.
SAS: sleep apnea syndrome ; AVSD : atrioventricular septal defect ; VSD : ventricular septal defect ; VSD : ventricular septal defect ; VSD : ventricular septal defect ; CNS: central nervous system ; GERD: gastro-esophageal reflux disease ; SMR ; Severe mental retardation.

	Current study (%)	Prevalence in literature (%)	References
ENT	24.06	38--78	[10].
Ophthalmologic	20	38--80	[10, 31].
CHD	16.92	44--58	[28, 35].
CNS	9.23	18--38	[10, 12, 34].
Gastroenterological	9.23	4--10	[15, 37].
Thyroid	9.23	28--40	[14, 15, 38].
Diabetes mellitus	3.08	4.3	[15].
Musculoskeletal	3.08	10--30	[39].
Urologic	1.54	3.2	[40].
Skin	1.54	1.9--39.2	[41].

Table 3. Prevalence of medical problems in children with Down syndrome.

	DS with comorbidities (n=133)	DS without comorbidities (n=74)	Pearson	*P*-value
Gender (% Male)	133 (59.4%)	74 (64.85%)	0.39082	ns
***Maternal age (year)**				
n=182				
Under 30	18	12	6.1863e-31	ns
30---40	45	36	1.423	ns
Over 40	48	23	1.7104	ns
***Consanguinity**				
n=186				
1st degree	18	11	8.1686e-30	ns
2nd degree	6	6	0.27437	ns
Non	90	55	0.052179	ns

Table 4. Gender, maternal age and parental consanguinity among Down syndrome (DS) patients with and without comorbidities
***** Missing data was eliminated

Ethical considerations

This study was approved by the Ethics and Deontology Council of the Tlemcen's University. All individuals were included in this study only after the Informed Consent of their parents or their responsible.

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