

Prevalence and Pattern of Associated Anomalies in Preliminary Working among Congolese Children with Down Syndrome: Analysis of 83 Patients and African Review

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Abstract

Background: Down syndrome (DS) is the most common chromosomal disorder in the world. The condition includes typical facial dysmorphism with intellectual disability and diverse associated visceral anomalies. DS is often diagnosed in Congo Brazzaville, but there are only a few significant reports of the condition. This preliminary study aimed to determine the prevalence and the pattern of DS associated anomalies in Congolese children.

Patients and methods: This work included patients with Down's syndrome (DS) provided from a congenital malformation series seen at the pediatric services (Neonatology and Intensive care) in University Teaching Hospital (UH) of Brazzaville for a period of five years (from January 2011 to January 2016). Some of the patients were newborns and some were older children.

It was a retrospective study based on the pediatric registries and records. The diagnosis of DS was based on clinical features. Systematic chest radiography was performed in cases of any associated anomalies and two-dimensional echocardiography with doppler in cases of cardiac defects. The scanner examination was made in cases of cerebral anomalies.

Results: During the study period, a total of 430 children with congenital malformations have been seen, from which 19.3% (83/430) with confidence interval (CI) 95%=[0.15-0.20] were identified with DS. Their age ranged from one day to 12 years. The mean age of the diagnosis of DS was seven days and 18 months for the discovery of associated anomalies. The male sex was prevalent with a sex ratio of 1.07. The anomalies associated with DS were present in 74.7% (IC 95%=[0.66-0.84]) of the patients. The most common anomaly was congenital heart defect (CHD), in 40.3% of associated anomalies in which the ventricular septal defect, atrio-ventricular septal defect and atrial septal defect were the prevalent lesions. In addition, the affected children were mainly exposed to acute bronchopneumopathy followed by brain and digestive infections.

Conclusion: The Down syndrome accounts for a significant portion of congenital malformations diagnosed in UH of Brazzaville with a high prevalence of associated CHD and an increased susceptibility to respiratory tract infections.

Keywords: Down syndrome; Trisomy 21; Associated anomalies; Congenital heart defects; Congo

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Introduction

Down syndrome also known as trisomy 21 is the most common chromosomal anomaly among newborns. Since the first description of the genetic condition in 1866 by John Langdon Down and the visualization of the additional chromosome 21 in 1959 by Lejeune and Jacobs, many studies and advances in patient management have been made on DS [1-3]. The current incidence is approximately 1/700 live births [4-6].

The affection is a combination of characteristic facial dysmorphic features (that often facilitate the diagnosis) and multiple visceral associated anomalies. It is also the commonest cause of mental deficiency.

In medical practice, genetic confirmation is performed by conventional karyotype, fluorescent *in situ* hybridization (FISH) and comparative genomic hybridization on array (aCGH) in way to visualize additional chromosome 21 (or a segment). However, rapid diagnosis in 48 hours is possible by FISH analysis [7,8]. Ultrasound examination and maternal serum screening (as α -fetoprotein, chorionic gonadotrophin, oestriol, PAPP-A) are proposed in antenatal (in the first and second trimester) [5,7,9].

The trisomy 21 may be full and free, translocation or mosaicism [7,10]. The disease is caused in majority (95% of cases) by a chromosomal non-disjunction during meiosis I more than during meiosis II [6,9]. The advanced maternal age (over 35 years old) so far is the main indexed causal factor for that chromosomal defect, but DS also happen in infants of younger women [3,4].

The condition is compatible with survival up to 60 years [11]. Therefore, an evolution towards various pathologies is usual. For example, the persons with DS have ocular problems such as poor visual acuity (6/10), myopia, astigmatism, strabismus, nystagmus, or cataract [3,12]. Autism is also reported. In addition, people affected from DS since the age of 40 years are more exposed to Alzheimer's disease with dementia (than in general population) [13]. Cases of acute leukemia are also reported [14].

In Congo, DS is frequently diagnosed but its epidemiological profile is unclear. We aimed in this preliminary work to precise the DS prevalence and the type of associated anomalies in children affected by the condition.

Patients and Methods

Patients

Patients with Down's syndrome (DS) have been listed from a series of congenital malformations seen at the Pediatric services (Neonatology and Intensive care) in the University Teaching Hospital Center (UHC) of Brazzaville during January 2011 to January 2016 (i.e. five years). The patients born or followed in UHC ranged from newborns to children.

Methods

It was a retrospective study based on the pediatric registries

and records. The diagnosis of DS was based on clinical features easily identifiable. Systematic chest radiography was performed in cases of any associated anomalies and two-dimensional echocardiography with doppler in cases of cardiac defects. The scanner examination was made in cases of cerebral anomalies. The study requires the ethics committee's approval (IRSSA Ethics commission approval, 026/MRSIT/IRSSA-DG/17).

Statistical analysis

Data are medians with intervals. The confidence interval has been considered to 95%. We used the Student's t-test= $P+/-1.96VP(1-P)/n$ with the SPSS 10 (SPSS statistics version 10.0).

Results

430 children with congenital malformations have been observed during the period of study, among which 83 were suffering from the DS. We note that, among the 4785 children examined in Neonatology service, in the year 2015, 11 were suffering from the DS.

The rate of prevalence of DS in neonatology service for 2015 was of 11/4785 cases of all newborns (i.e. 0.23%). Among the 430 children suffering from various congenital malformations, the prevalence of DS was of 19.3% (83/430) with confidence interval (CI) 95%=[0.15-0.20]. Their age ranged from one day to 12 years.

The mean age for DS diagnosis was of seven days with extremities of 1 to 25 days and the mean age for the discovery of associated anomalies was of 18 months with extremities of twenty six days to 144 months (i.e. 12 years). The male sex was predominant, 51.8% (43/83), and the male to female ratio was 1.07 (43/40). All the children lived in urban departments of Brazzaville.

Associated anomalies observed in two forms (congenital and acquired) were present in 74.7% (62/83) (IC 95%=[0.66-0.84]) of the cases of DS (**Figure 1**). Congenital cardiac defects occurred in 40.3% of associated anomalies (i.e. 30.12% of DS). The distribution of the CHD types (which were only single lesions) is reported in **Table 1**. The first acquired anomaly was acute bronchopneumopathy in 32% of associated anomalies (i.e. 24.09% of DS), followed by encephalopathy and gastroenteritis (**Table 1**).

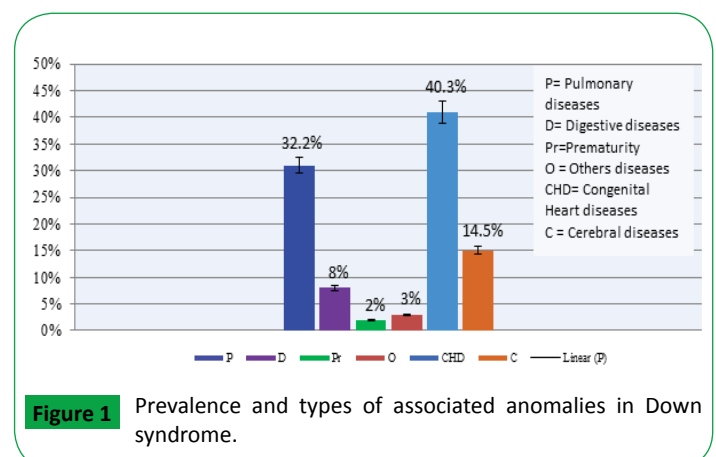


Table 1 Details and percentage of Down syndrome associated anomalies.

Anomalies and types of lesions	Number	AAP (%)	DSP (%)
		n= 62	n= 83
Cardiac	25	40.3	30.12
Interventricular septal defect	15	(24.1)	-
Atrial septal defect	5	(8)	-
Atrio ventricular septal defect	3	(4.8)	-
Pulmonary artery stenosis	2	(3.2)	-
Respiratory	20	32.2	24.09
ABP	20	32.2	-
Cerebral	9	14.5	10.84
Encephalopathy	4	(6.45)	-
Hydrocephaly	3	(3.6)	-
Convulsions	2	(3.2)	-
Digestive	5	8	6.02
Gastroenteris	2	(3.2)	-
Megacolon	1	(1.6)	-
Refusal to feed	2	(3.2)	-
Prematurity	1	2	1.2
Others	2	3	2.4
Total	62/83	100.00	74.69

AAP: Associated Anomalies Percentage; DSP: Down Syndrome Percentage;
 VSD: Ventricular Septal Defect; AVSD: Atrioventricular Septal Defect;
 ASD: Atrial Septal Defect; ABP: Acute Bronchopneumopathy

Discussion

The Down syndrome is a clinically diagnosable condition. Many DS studies in Africa are only based on clinical diagnosis [1,15,16]. Interestingly, an original study using digital facial analysis technology based only on photography's images and clinical information (performed in a large cohort of diverse populations), allows to clinically diagnose DS with a sensitivity of 0.961, a specificity of 0.924 and an accuracy of 0.943 [11]. In current medical practice, the clinical diagnosis is in general possible in 73 to 100% of the cases of DS [6,17].

There are few published studies in Africa about the prevalence of DS. The first rate prevalence of 1.16/1000 live births was reported in 1982 in Nigeria [2,11,17,18]. In South Africa, the prevalence varies according to the area and it accounts for 0.8 to 2.1/1000 of the live births [17]. In Tunisia, the estimated prevalence is 0.98/1000 pregnancies [9].

In our work, the estimated prevalence rate of DS (from one year in neonatology) was of 11/4785 of newborns (i.e. 0.23%) and the prevalence of DS from all congenital malformations was of 19.3% of the patients.

Concerning the age and the sex of the patients, the mean age for DS diagnosis in our work was earlier, seven days because DS infants came in part from neonatology where the condition was clinically detected by pediatrician's right after their birth. But the mean age for diagnosis of associated anomalies was older (18 months). The latter data were quite similar to the review. In Benin, the mean age of diagnosis of associated visceral malformations was of 18.8 months. In Morocco, the mean age for CHD for example was younger (9.5 months) [10,19]. The difference may be based on the fact that in the latter country, there is an active medical

program for children with Down syndrome and the diagnosis is also based on karyotype analysis [6,10].

About the sex gender, our results and published literature show that the two sexes are concerned, with a predominance in male gender [3,4,11,19-21].

The DS associated anomalies identified in many studies are comorbidities that increase the risk of mortality of DS children. Out of skeletal deformities, gastrointestinal malformations or renal defects, congenital heart defects (CHD) is one of the most associated congenital malformations in DS. The prevalence of global CHD in DS and the type of lesions are approximately the same in African countries. According to the literature data, the CHD is present in between 40 to 63.5% of the children having DS [1,10,15,16,19]. For example, in Rwanda study (based on cytogenetic analysis), 53.9% (48/89) of DS patients had CHD (isolated or multiple) and 46.06% (41/89) of DS had absence of CHD [22]. In one Moroccan study, the CHD accounted for 30.5% of DS [3].

Our findings were in agreement with the reported studies [3,4]. In total, the associated anomalies have been identified in 74.7% of SD, and CHD was the most common associated anomaly with a rate prevalence of 40.3% (i.e 30.12% of DS). The most common CHD types were: ventricular septal defect (VSD), atrioventricular septal defect (AVSD) and atrial septal defect (ASD). These three first CHD lesions were consistent with others African studies (Egyptian, Moroccan, Libyan or Benin reports) [4,3,10,21]. But there is a variation in the frequencies of the types of CHD among years and countries. For example in Northern and West African SD (Nigeria, Algeria, Morocco or recently study in Benin) AVSD ranked the first place of CHD in DS [15,10,19,23]. While isolated VSD is more prevalent in Rwanda or in Benin previous study such

as in China [21,22,24]. In one Nigerian study, the single VSD had also a high proportion after the patent ductus arteriosus [16]. The cardiovascular profile in DS and the reasons of the differences in percentage of the CHD lesions are poorly known.

However, the consequence in all countries is that these associated heart defects increase the morbidity and mortality of DS, mainly in the two first years of life [10,25]. All these heart defects found in our series and review can be surgically corrected with satisfactory results.

Along with genetic factors, many associated risk factors among DS persons are indexed on the occurrence of those CHD. It concerns environmental factors, maternal risk factors such as: stress, smoking during early pregnancy, obesity, parity, deficit in folic acid or parental consanguinity [4,26].

The congenital gastrointestinal anomalies are also frequently observed in DS with the high percentage of 77% [27]. The megacolon found in our series is not exceptional because it is one of the clinical signs of Hirschsprung's disease (due to aganglionosis in the distal bowel) also associated with DS [27-29]. Prematurity in this work was found only in one case. Usually, pregnancies with DS are at greater risk of prematurity (before 36 weeks) [30].

Concerning acquired infections in our series, it was the second associated anomaly.

Respiratory tract infections of the type of acute bronchopneumopathy were the commonest form of infection with a prevalence rate of 32% (20/62) of associated anomalies, followed by encephalopathy and gastroenteritis (**Table 1**).

The high predisposition to infections and autoimmune diseases in persons with DS is known because the condition is associated to immune system and anatomical malformations (as thymic hypoplasia, lung defect, CHD) that increase the risk of infections [20,31]. In addition, DS subjects have dysfunctions in lymphocytes subpopulations [31-33] that also increased the risk of infection especially in respiratory tract (lungs and airways), in otorhinopharyngeal sphere or in oral and teeth areas [31,33].

Antenatal infections are observed in 49.5% of DS in some studies [4]. In postnatal period and in children, the data of associated infections in the review is approximately in accordance with our findings. Indeed, in an Egyptian study, associated infections in DS children (between the age of 6 months and eleven years) were detected in 38% of the patients with predominance of lower respiratory tract infections (51.1%) followed by urinary tract, eyes (11.8%), blood stream (7.4%) and skin (1.5%) infections. In the latter study, the causative pathogenic agents of infections were diverse (bacterial, fungal or viral) [20].

Other associated pathologies acquired seen in the Congolese DS, as acute leukemia (AL) have been reported in previous study [14]. AL is known to be 10 to 15 times more frequent than in normal population [33]. The other anomalies reported in the review concern kidneys and endocrine deficit (especially hypothyroidism, obesity, diabetes) [33].

At the end of this preliminary work, we note that our study has limitations because the DS diagnosis was based only on clinical

phenotype. The parental age not mentioned in the records will be specified in another prospective study in progress.

Conclusion

The study has provided significant preliminary data (about prevalence and the pattern of DS associated anomalies) which basically reflect others African studies. The Congolese children with DS have a high rate of CHD and an increased susceptibility to infections especially in respiratory tract. These results are important in the management of DS in order to perfect the lifestyle of Congolese children affected by the condition.

In view of the data of this work, we will set up as in others countries [8,21] a program of medical genetic consultations for persons with Down syndrome and their families. The main goal of this approach is to improve DS management and family counseling in recurrent cases.

What does this work bring? To the extent that there are not enough studies on African persons with DS, interestingly, this study draws a new epidemiological profile on DS associated anomalies in a given Africa country.

Authors' Contributions

Analyzed the data: EM, HP. Statistical calculation: ACN, YVYM. Designed the study and draft the paper: HP.

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