THE PUBLISHING HOUSE
OF THE ROMANIAN ACADEMY

MEDICINE
Research article

CRANIO-FACIAL DYSMORPHISM AND DEVELOPMENTAL DELAY IN ROMANIAN CHILDREN WITH TRISOMY 21

RALUCA MARIA VLAD[1], PAULA GRIGORESCU SIDO[2], SIMONA BUCERZAN[2], CAMELIA AL-KHZOUZ[2], IOANA NAŞCU[2], EUGEN PASCAL CIOFU[1] and DUMITRU ORASEANU[1]

[1] Department of Pediatrics, "Grigore Alexandrescu" Emergency Children's Hospital, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2] Department of Medical Genetics, Emergency Children's Hospital, "Iuliu Haţieganu", University of Medicine and Pharmacy, Cluj-Napoca, Romania
Corresponding author: Raluca Maria VLAD, E-mail: ralu_neagoe@yahoo.com

Received June 10, 2013

Trisomy 21 is the most frequent autosomal chromosomopathy. The clinical picture includes dysmorphism, developmental delay and malformative syndrome. At present time, in Romania, the cytogenetic diagnosis is delayed. The aim of this study was to evaluate the dysmorphism in correlation with the cytogenetic findings and to asses the developmental delay. We conducted an observational study that included 136 patients with trisomy 21 recruited from the Department of Medical Genetics, Emergency Children's Hospital, Cluj-Napoca and the Department of Pediatrics, "Grigore Alexandrescu" Emergency Children's Hospital, Bucharest. The patients were evaluated recording the clinical characteristics, the somatic and intellectual development. In 91.2% of the cases the diagnosis of regular trisomy 21 was established. The cariogram was performed late, at a mean age of 1 year 6 months. 61% of patients were boys; the mean age was 3 years 6 months. All patients displayed dysmorphic features. The most frequent clinical findings were: upslanting palpebral fissures (94.19%), hypothelorism (80.1%) and low set/small/malformated ears (79.4%). No significant differences regarding the dysmorphic features were found between regular and mosaic trisomy 21. In infants, the weight gain was delayed. In children ≥ 1 year the delay was predominantly in height gain and 37.3% were overweight. The mean IQ was 45. A significant number of Romanian patients with Down phenotype do not benefit from an early genetic diagnosis. Our study summarized the elements of the cranio-facial dysmorphism, somatic and intellectual development of children with trisomy 21. The somatic developmental delay varied with age. The intellectual delay was recorded for all patients. No significant differences were found in relation to the cytogenetic diagnosis.

Key words: trisomy 21, dysmorphism, developmental delay.

INTRODUCTION

Trisomy 21 is the most frequent autosomal chromosomopathy. Although the facial dysmorphism is present since birth, as far as our country is concerned, the cytogenetic diagnosis is reached late in most cases, due to a low number of centers where cariogram is performed[1].

The clinical picture includes dysmorphism, malformative syndrome and developmental delay. The most frequent features of the specific dysmorphism are: round face with midface hypoplasia, upslanting palpebral fissures[2–4], epicantus[4–6], small mouth[2,5], with spontaneous protrusion of the tongue[2,5,6], low set ears[3,6,7]. The somatic and pubertal developmental delay are less severe than the intellectual one. Patients present with low height and become overweight in time[3]. The IQ varies between 20 and 75[7].

The cytogenetic diagnosis in children with Down phenotype may be: regular trisomy 21 (90-95%), mosaic trisomy 21 (1-2.5%) or unbalanced/ robertsonian translocation (2-4%) [3,4,7,8].

Considering that clinical observation in the latter years showed some changes in the classic clinical picture and that there are no studies on this topic in the Romanian medical literature.

We aimed to evaluate the cranio-facial dysmorphism in correlation with the cytogenetic findings and to asses the developmental delay of patients with trisomy 21.

MATERIAL AND METHOD

We conducted an observational study that included 136 patients with trisomy 21 recruited from two university clinics: 126 from the Department of Medical Genetics, Emergency Children's Hospital, Cluj Napoca and 10 from the Department of Pediatrics, "Grigore Alexandrescu" Emergency Children's Hospital, Bucharest.

The diagnosis of trisomy 21 was suspected clinically and confirmed through cytogenetic testing (band karyotype).

For each patient the following parameters were recorded: sex, age at clinical diagnosis, at cytogenetic diagnosis and at the last visit, county of residence, auxological data at birth and at the moment of inclusion and clinical data regarding the facial dysmorphism.

For the developmental delay, the weight and height were evaluated using OMS percentiles for patients under the age of five[9] and Center for Disease Control (CDC), USA percentiles for patients older than five years[10]. The ponderal index (PI) was calculated for infants. For patients older than one year we used percentiles for weight, height, BMI and the standard deviation score for height, calculated based on CDC percentiles using EpiInfo. The development quotient was evaluated < 7 years and the intelligence quotient ≥ 7 years. Microsoft Excel and SPSS were used for statistical analysis and the chi-square test for statistical comparison, considering $p<0.05$ statistically significant.

RESULTS

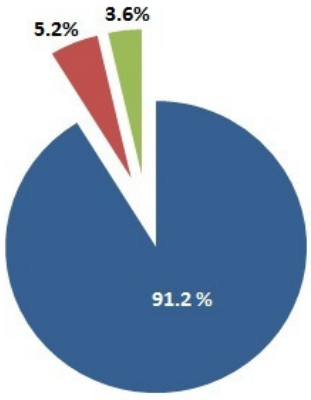
The clinical diagnosis of Down syndrome was made at birth in the majority of cases (97.8%), but the cytogenetic diagnosis took a mean of 1 year 6 months, with variations from 2 days to 16 years 5 months (Table 1). The cytogenetic distribution of the patients is illustrated in Figure 1.

Table 1

The patient distribution according to the age at cytogenetic diagnosis

Age at cytogenetic diagnosis	n	%
< 1 month	16	11.8
1– 6 months	62	45.6
6 months – 1 year	23	16.9
1 – 3 years	16	11.8
3 – 5 years	5	3.7
5 – 7 years	4	2.9
> 7 years	10	7.3

The mean age of the patients at the time of the study was 3 years 6 months, with variations from 7 days to 16 years 5 months.



Combination of cytogenetic anomalies		5
Regular trisomy 21/translocation (2q,1p)	47,XY,21+/t(2q;1p) 47,XX,21+/t(2q;1p)	2
Regular trisomy 21/duplication of heterocromatine region 9q12	47,XY,21+/9qh+	1
Regular trisomy 21/inversion on 9th chromosome	47,XY,21+/inv(9)(p11;q13)	1
Regular trisomy 21/Klinefelter	47,XY,21+/47,XXY	1

Fig. 1. The patient distribution according to the cytogenetic findings.

The male/female ratio was 1.56/1 ($p<0.01$).

The geographic distribution of the cases is represented in Figure 2.

Fig. 2. The geographic distribution of trisomy 21 children.

The elements of facial dysmorphism described in studied patients are synthesized in a decreasing order of their prevalence in Table 2. We compared their frequency in regular trisomy 21 and mosaic, and in regular trisomy 21 and combinations of cytogenetic anomalies and found no statistically significant differences ($p>0.05$).

Table 2
The characteristics of the dysmorphism in the studied group

Clinical feature	Regular trisomy 21 (n_1=124)		Mosaic (n_2=7)		Combination of cytogenetic anomalies (n_3=5)		Total (n_4=136)		În the medical literature
	n	%	n	%		%	n	%	
Upslanting palpebral fissures	119	96	6	85.7	4	80	129	**94.9**	63-83.2% [2-4,11]
Hypotelorism	98	79	6	85.7	5	100	109	**80.1**	[3]
Low set/small/malformated ears	97	78.2	6	85.7	5	100	108	**79.4**	[3,7]
Round-shaped face	88	71	4	57.1	4	80	96	**70.6**	[2-5]
Spontaneous protrusion of the tongue	85	68.5	5	71.4	4	80	94	**69.1**	[5,6]
Bilateral medial epicantus	75	60.5	4	57.1	4	80	83	61	61-93.7% [5,11]
Unilateral medial epicantus	9	7.3	0	0	0	0	9	6.6	[5]
Uni/bilateral medial epicantus (total)	84	67.7	4	57.1	4	80	92	**67.6**	[5]
Small, broad nose	74	59.7	5	71.4	3	60	82	**60.3**	74.7% [5]
Short neck	73	58.9	3	42.8	3	60	79	**58.1**	72.6% [5]
Midface hypoplasia	64	51.6	2	28.6	4	80	70	**51.5**	[2]
Brachycephaly	30	24.2	3	42.8	3	60	36	26.5	90.6% [5]
Low set hairline	27	21.8	0	0	0	0	27	19.9	[3,5]
Micrognatism	25	20.2	1	14.3	0	0	26	19.1	[5]
Microstomia	24	19.4	0	0	1	20	25	18.4	[2,5]
Microcephaly	17	13.7	1	14.3	1	20	19	14	[5,7]
High arched palate	12	9.7	1	14.3	2	40	15	11	[4]
Brushfield spots	7	5.6	0	0	0	0	7	5.1	0-90% [2,3,6,11]
Pterigium coli	3	2.4	0	0	1	20	4	2.9	61.1% [5,12]
Synophrys	4	3.2	0	0	0	0	4	2.9	

The birth weight of the patients varied between 1010 and 4400 grams, average: 2904 grams; 17.6% had low birth weight (< 2500 g). The birth length varied between 38 and 58 cm, average: 49.7 cm; in 43.4% the length did not exceed 50 cm at birth (Figure 3).

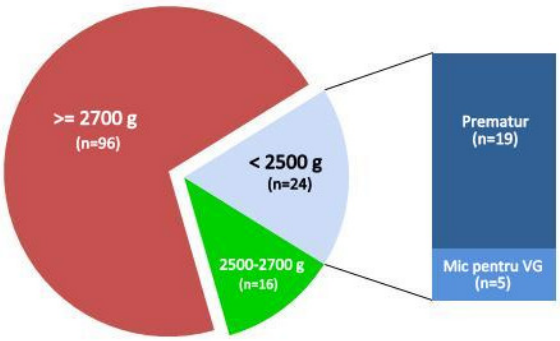


Fig. 3. Auxologic data of trisomy 21 patients at birth.

The somatic development of the patients was evaluated at the moment of inclusion (Table 3).

Nine patients were at a pubertal age: ≥ 13 years for boys and ≥ 12 years for girls[13]. Seven of these (2 boys and 5 girls), representing 77.7% of the group, had a pubertal delay.

A motor delay was described in 82.4% of the cases.

The development/intelligence quotient varied from 20 to 72, average: 45.

DISCUSSION

The analysis of the group of patients showed an increased predominance of the male gender (M/F=1.56/1); this observation differs from some data in the literature that communicate a light predominance of the male gender (M/F=1.15/1)[14].

Although for the majority of patients a clinical diagnosis was made since birth, the cytogenetic diagnosis of trisomy 21 was delayed. This is the consequence of a difficult access to medical units with experience and technical means to perform genetic testing. The percentage of regular trisomy 21 was 91.2%, among cited limits (90–95%) [3,7,8]; the mosaic was more frequent (5.2 *versus* 1–2.5%[3,7,8]) and there were no cases of robertsonian translocation. Instead, a number of combinations of cytogenetic anomalies were described, autosomal and gonosomal in four and one patient respectively, representing 3.6% (Figure 1).

Table 3

Somatic development of patients with trisomy 21

	0 – 1 month (n_1=4)		1 month – 1 year (n_2=51)		≥ 1 year (n_3=81)	
	n	**%**	**n**	**%**	**n**	**%**
A. Weight						
Normal weight (PI: 0.9-1.1)	2	50	7	**13.7**	11	**13.6**
Underweight (PI<0.9)						
a) Malnutrition 1st grade (PI: 0.89-0.76)	2	50	21	41.2	-	-
b) Malnutrition 2nd grade (PI: 0.75-0.60)	0	0	16	31.4	-	-
c) Malnutrition 3rd grade (PI <0.60)	0	0	5	9.8	-	-
Total underweight patients	2	50	42	**82.4**	40	**49.4**
Overweight (<1 year:PI >1.1; ;≥1 year:BMI pc.85-95)	0	0	2	**3.9**	11	**13.6**
Obese (BMI > pc 95)	-	-	-	-	19	**23.5**
Total patients with excessive weight	0	0	2	3.9	30	37
B. Height						
Normal height (> -1 SD)	4	100	23	**45.1**	20	**24.7**
Low height						
a) -1 → -2 SD	0	0	12	23.5	22	27.2
b) -2 → -3 SD	0	0	5	9.8	20	24.7
c) > - 3 SD	0	0	11	21.6	19	23.5
Total patients with low height	0	0	28	**54.9**	61	**75.3**

All patients had clinical features of the facial dysmorphism. Compared to the previously communicated data, some clinical characteristics have higher incidence: upslanting palpebral fissures (94.9% *versus* 63-83.3%[2-4,11]) and some have lower incidence: bilateral medial epicantus (61% *versus* 61-93.7%[5,11]), small, broad nose (60.3% *versus* 74.7%[5]), short neck (58.1% *versus* 72.6%[5]), brachycephaly (26.5% *versus* 90.6%[5]), Brushfield spots (5.1% *versus* 0-95% [2,6,11]) or *Pterigium coli* (2.9% *versus* 61.1%[5,12]) (Table 2).

Children with trisomy 21 have an average birth length of 48-49 cm and the birth weight with 300-450 g lower than normal weight for corresponding gestational age[3]. The birth weight and length of the patients in our group were similar to cited data. The analysis of the somatic parameters (Table 3) showed that only 14.5% of patients <1 year and 8.6% of patients ≥ 1 year had normal for age auxological parameters. In infants the weight gain was delayed. In children ≥ 1 year the delay was predominantly in height gain and 37.3% were overweight; it is common knowledge that, frequently, these patients develop obesity in time[3]. All in all, 66.9% of patients had a height gain delay. The maximum height recorded in the literature is 155 cm in male and 146 cm in female[3,9,10].

The pubertal delay was more frequent in girls. As the intellectual development is concerned, low to moderate retardation predominated, data in agreement to the literature[7].

CONCLUSIONS

A significant number of Romanian children with Down phenotype do not benefit from an early cytogenetic diagnosis, the mean age for genetic confirmation of trisomy 21 being 1 year and 6 months. Nationwide, efforts should be made in order to overcome this mischief.

Our study summarized the elements of the cranio-facial dysmorphism of children with trisomy 21. The most frequent clinical findings were: upslanting palpebral fissures (94.19%), hypothelorism (80.1%) and low set/small/malformated ears (79.4%).

The somatic developmental delay varied with age. In infants, the weight gain was delayed. In children ≥ 1 year the delay was predominantly in height gain and 37.3% were overweight.

The intellectual delay was recorded for all patients. No significant differences were found in relation to the cytogenetic diagnosis.

REFERENCES

1. Chen H., Genetics of Down Syndrome in Medscape Reference, 2011: 1-7;

2. Dourmishev A.L., Janniger Camila: Down Syndrome in Medscape Referance, 2010: 1-4;
3. Grigorescu-Sido Paula, Cromozomopatii autozomale – Trisomia 21 (boala Langdon Down). In Grigorescu-Sido Paula (eds.):Tratat elementar de pediatrie, vol. IV, Casa Cartii de Stiinta, Cluj Napoca, 2000: pp. 17-19;
4. Hall Judith, Chromosomal Clinical Abnormalities. In Behrmann R.E., Kliegman R.M., Jenson H. B.(eds.): Nelson Textbook of Pediatrics , 17th Ed., Saunders, 2003: pp. 382-386;
5. Sureshbabu R., Kumari R. *et al.*, Phenotypic and dermatological manifestations in Down Syndrome in Dermatology Online Jurnal, 2011: 1-5;
6. Firth Helen, Genetics. In Tasker R.C., McClure R.J., Acerini C.L.: Oxford Handbook of Pediatrics, Oxford University Press, 2008: pp. 904-909;
7. Patton M.A., Genetics. In Mcintosh N., Helms P.J., Smyth R.L., Logan S. (eds.): Forfar & Arneil's Texbook of Pediatrics 7th Ed., Churchill Ligingstone, 2008: pp. 1234-1245;
8. Mandava S., Koppaka N., Bhatia V. *et al.*, Cytogenetic analysis of 1572 cases of Down syndrome: a report of double aneuploidy and novel findings in an Indian population, Genet Test Mol Biomarkers, 2010: 499-504;
9. www.who.int/childgrowth/standards/en;
10. www.cdc.gov/growthcharts/clinicalcharts.htm;
11. Kim J.H., Hwang j.M., Kim H.J. *et al.*, Characteristic ocular findings in Asian children with Down syndrome, Eye, 2002:710-714;
12. Connor J.M, Ferguson-Smith M.A., Essential Medical Genetics, 3rd Ed., Blackwell, Oxford, 1993: pp. 117-119, pp. 131-135;
13. Grigorescu-Sido Paula, Bolile gonadelor – Pubertatea intarziata (Retardul pubertar). In Grigorescu-Sido Paula (eds.):Tratat elementar de pediatrie, vol. IV, Casa Cartii de Stiinta, Cluj Napoca, 2000: pp. 248-258;
14. Izquierdo N.J., Townsend W., Down Syndrome in Medscape Referance, 2010: 1-3.