MÆDICA - a Journal of Clinical Medicine

ORIGINAL PAPERS

Clinical relevance of cytogenetics to pediatric practice. Postnatal findings of Patau syndrome – Review of 5 cases

Vasilica PLAIASU[a], MD; Diana OCHIANA[a], biol.; Gabriela MOTEI[a], biol.; Ioana ANCA[b], MD, PhD; Adrian GEORGESCU[b], MD, PhD

[a]Genetics Department, IOMC "Alfred Rusescu", Bucharest, Romania
[b]Pediatrics Department, "Carol Davila" University of Medicine and Pharmacy, IOMC "Alfred Rusescu", Bucharest, Romania

ABSTRACT

Introduction: Patau syndrome (trisomy 13) is one of the most common chromosomal anomalies clinically characterized by the presence of numerous malformations with a limited survival rate for most cases. Babies are usually identified at birth and the diagnosis is confirmed with genetic testing.

Materials and methods: In this review we outline the clinical and cytogenetic aspects of trisomy 13 and associated phenotypes for 5 cases analyzed in the last 3 years, referred to our Clinical Genetics Department. For each child cytogenetic analysis was performed to determine the genetic variant; also, the patients were investigated for other associated malformations (cardiac, cerebral, renal, ocular anomalies).

Discussion: All 5 cases presented multiple malformations, including some but not all signs of the classical clinical triad suggestive of Patau syndrome. The cytogenetic investigation confirmed for each case the suspected diagnosis and also indicated the specific genetic variant, this being a valuable information for the genetic counselling of the families.

Conclusion: The application of genetic analysis can increase diagnosis and prognosis accuracy and have an impact on clinical management.

Keywords: trisomy 13, Patau syndrome, polydactyly, cleft palate, microphthalmia, genetics

INTRODUCTION

Trisomy 13 or Patau syndrome is a clinically severe condition associated with low survival rates because of malformations of the central nervous system (CNS), cardiac, circulatory and urogenital systems. This syndrome occurs in all ethnicities and equally affects both males and females. There are a few genetic variants of this disorder. The most frequent one is free trisomy 13 (1/12000) (1) and is characterised by the presence of an extra chromosome 13 in each cell of the body. A small percentage of

Address for correspondence:
Vasilica Plaiasu, MD, IOMC "Alfred Rusescu", 120 Lacul Tei Blvd., District 2, Bucharest, Romania
email address: vasilica.plaiasu@gmail.com

cases have a mixed population of cells, some presenting normal karyotype and the others having an extra copy of the chromosome 13. The third variant is represented by a Robertsonian translocation (1/56000-1/80000) (1) when the extra chromosome 13 is attached to another chromosome 13 or other acrocentric chromosome. Trisomy 13 can also occur when a person has just a part of an extra chromosome 13 in the cells, giving rise to partial trisomy 13.

In practice, Patau syndrome is recognized generally by the presence of a *clinical triad* of signs: microphtalmia, polydactyly and cleft palate. ❑

MATERIALS AND METHODS

This is a retrospective review of the cases with Patau syndrome phenotype selected from the cohort of subjects referred to our clinical department over the last three years (2007-2009). Peripheral blood specimens have been collected from all patients and cytogenetic analysis was performed on GTG-banded metaphase spreads prepared from phytohemagglutinin (PHA)-stimulated peripheral blood lymphocytes. The harvesting of the cultures was done after 72h of incubation and for each case 30 GTG-banded metaphases were analyzed using LUCIA Cytogenetics System. The karyotype results were elaborated according to ISCN 2009 standards (International System for Human Cytogenetic Nomenclature).

All morphometric data of the patients were compared with normal morphometric measurements for the same age and gender, using CDC growth charts (2).

The selected cases have incomplete evaluation because of early death (two patients) or incompliance of their families (three patients). ❑

CASE REPORTS

Case 1

The patient is a 6 days old male. *Family history*: mother of 30 years old with 2 miscarriages in the first trimester. *Birth*: 33 weeks gestational age, caesarean delivery, weight 2500 g (5th centile). *Clinical features*: microcephaly, frontal crease, down-slanting palpebral features, low-set ears, broad nasal bridge, median posterior cleft palate, single palmar crease, cryptorhidia, systolic heart murmur, dextrocardia. *Investigations*: cystic aspect of the grey matter observed by transfontanelar ultrasound. *Evolution*: severe; death at 2 weeks of age. *Karyotype result*: 47,XY,+13 (free trisomy 13) (Figure 1a).

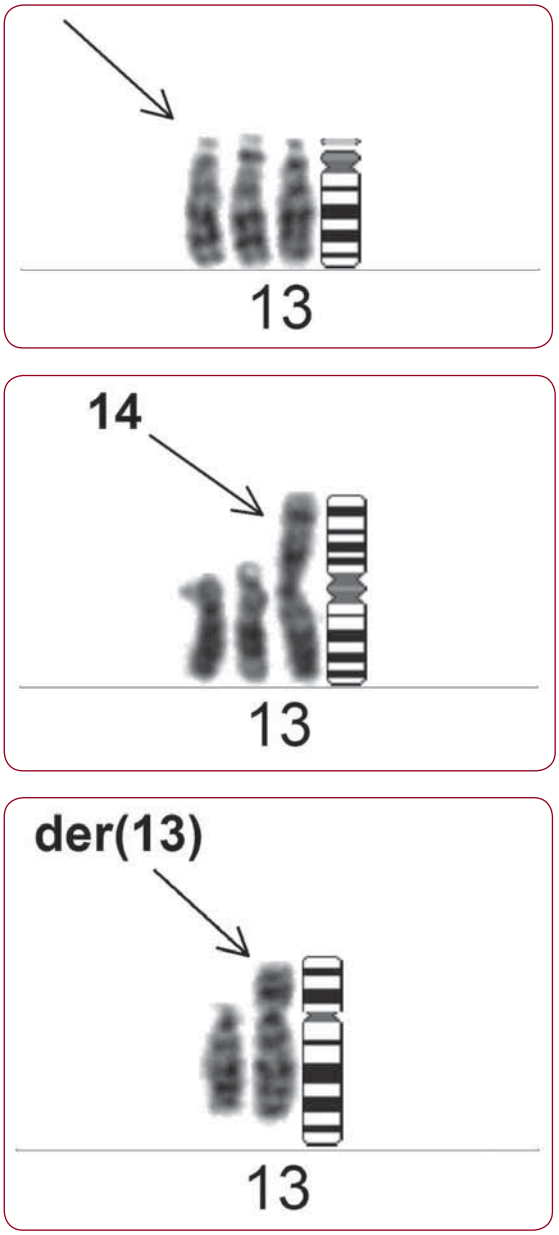

FIGURE 1. a) free trisomy 13 with the idiogram of G-banding pattern for normal chromosome 13 (cases 1,3 and 4); b) Robertsonian translocation t (13;14) with corresponding idiogram (case 5); c) partial trisomy 13 with idiogram of the derivative chromosome 13 (case 2)

Case 2

The subject is a male evaluated at the age of 3 months. *Family history*: nonconsanguineous parents, 25 years old mother, 27 years old father. *Birth*: 40 weeks gestational age, caesarean delivery (hypertensive mother), Apgar score 7,

weight 3450 g (50th centile), length 52 cm (75th centile), occipitofrontal circumference (OFC) 34.5 cm (25th centile). *Clinical features at age of 3 months*: weight 7500g (95th centile), length 70 cm (>90th centile), OFC 41 cm (50th centile), postaxial polydactyly for all limbs (Fig.2), cleft lip and palate, single palmar crease, hydrocele on the right side, systolic heart murmur and no neurodevelopmental delay. *Karyotype result*: 46,XY,der(13) (Fig.1c); parental karyotypes were not performed due to their refusal of the analysis.

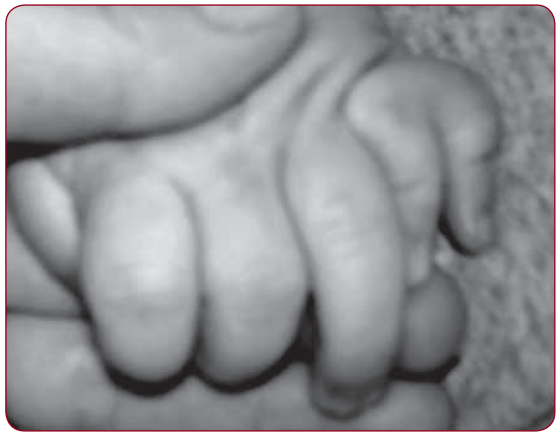

FIGURE 2. Postaxial polydactyly of the left hand

Case 3

This patient, a female, was examined at 2 weeks of age. *Family history*: mother of 33 years old, father of 34 years old. *Birth*: 40 weeks gestational age, vaginal delivery, Apgar score 7, weight 3600 g (50th centile), length 53 cm (90th centile). *Clinical features*: microphthalmia, vertex alopecia (Fig.3), hirsutism, median posterior cleft palate (Fig.4), broad nasal bridge, trilobed aspect of nose tip, low-set ears, no polydactyly, ambiguous external genitalia with scrotal appearance of labia majora, axial hypotonia combined with spastic extremities. *Investigations*: patent ductus arteriosus and atrial septal defect at echocardiography, double kidney on the left side at abdominal echographic evaluation. *Karyotype result*: 47,XX,+13 (free trisomy 13).

Case 4

The patient is a newborn male (3 days old). *Family history*: unknown (abandoned child). *Birth*: unknown. *Clinical features*: broad nasal bridge, low-set ears, postaxial polydactyly of the hands, omphalocele, heart murmurs. *Evolution*: died at the age of one week. *Karyotype result*: 47,XY,+13 (free trisomy 13).

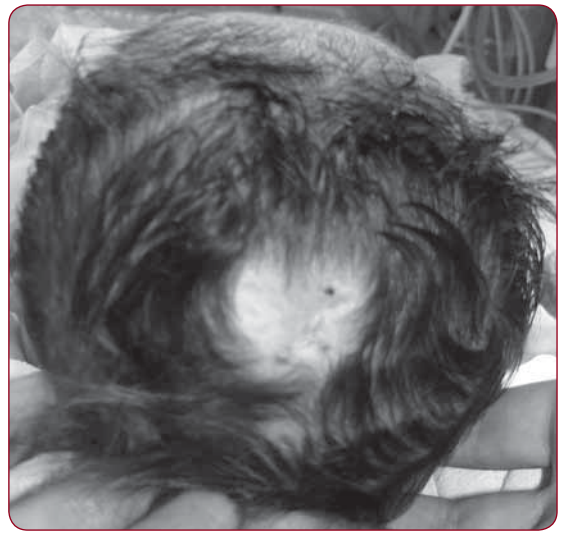

FIGURE 3. Vertex alopecia

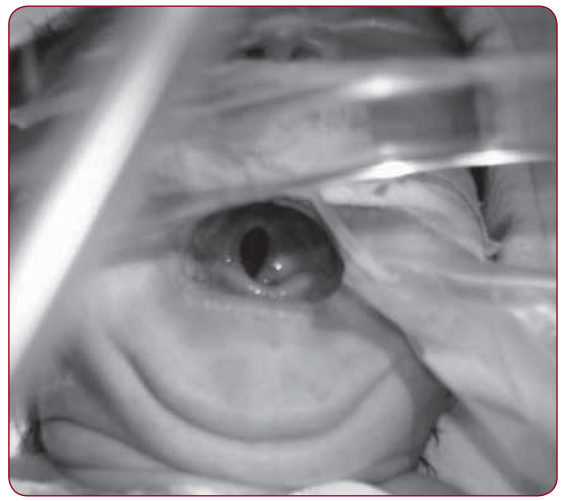

FIGURE 4. Cleft palate

Case 5

The subject is a 7 days old female. *Family history*: second child of a nonconsanguineous couple, mother of 32 years old; the patient has a healthy older sibling. *Birth*: 38 weeks gestational age, vaginal delivery, Apgar score 7, weight 2500 g (5th centile), length 49 cm (50th centile), OFC 32 cm (5th centile). *Clinical features*: dysmorphic facies with bilateral microphthalmia, vertex alopecia, bulbous nose tip (Fig.5), micrognatia, low-set ears, postaxial polydactyly of the hands. *Investigations:* normal on echocardiography and abdominal echography. *Karyotype result*: 46,XX,rob(13;14)(q10;q

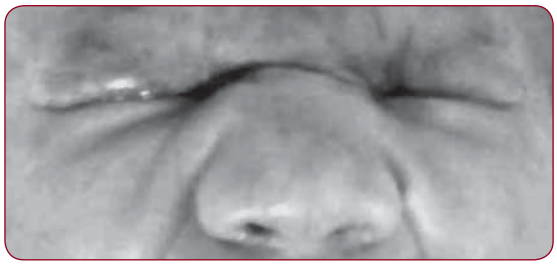

FIGURE 5. Short palpebral fissures, bulbous nose.

10),+13 (Fig.1b); mother's karyotype was normal; the father refused the investigation. ❑

DISCUSSION

The clinical spectrum of defects seen in our five cases (suggestive dysmorphic features, polydactyly and visceral malformations) indicates at first glance trisomy 13 (Table 1).

For cases 1, 3 and 4 was no need for the karyotype of the parents. Although the father of the patient 5 refused any further investigation for himself, paternal karyotyping should be arranged because a parent carrying a balanced Robertsonian translocation involving chromosome 13 is at risk of future recurrence of Patau syndrome. Also, the cytogenetic analysis for the parents of case 2 is very important to determine the origin of the extra material from the derivative chromosome 13 (Table 2). Considering the karyotype result combined with the clinical features suggestive of Patau syndrome, case 2 is likely to have a partial trisomy 13; unfortunately the child's parents refused any other further investigations. Partial trisomy 13 has a variable phenotypic expression and could result from a parental reciprocal translocation, parental pericentric inversion or de novo direct duplication.

Most common features of trisomy 13	*Case 1*	*Case 2*	*Case 3*	*Case 4*	*Case 5*
Craniofacial features					
scalp defects	-	-	+	-	+
microphtalmia	+	-	+	-	+
anophthalmia	-	-	-	-	-
low-set ears	+	-	+	+	+
cleft lip	-	+	-	-	-
cleft palate	+	+	+	-	-
bulbous nose	+	-	+	+	+
hypotelorism	-	-	-	-	-
micrognatia	-	-	-	-	+
microcephaly	+	-	-	-	-
Limb abnormalities					
polydactyly	-	+	-	+	+
rocker-bottom feet	-	-	-	-	-
single palmar crease	+	+	-	-	-
Genitalia abnormalities	+	-	+	-	-
Omphalocele	-	-	-	+	-
Congenital heart defects	+	+	+	+	-
Renal abnormalities	-	-	-	+	-
CNS abnormalities	+	-	-	-	-

TABLE 1. Most common features of trisomy 13 (the clinical signs that make up the classical triad for the recognition of Patau syndrome are marked in the table)

Cases	Age	Gender	Karyotype (ISCN 2009)	Origin
1	6 days	male	47,XY,+13	*de novo*
2	3 months	male	46,XY,der(13)	*?*
3	2 weeks	female	47,XX,+13	*de novo*
4	3 days	male	47,XY,+13	*de novo*
5	7 days	female	46,XX,rob(13;14)(q10;q10),+13	*?*

TABLE 2. Karyotype results for the 5 cases encountered

The clinical triad of signs (microphtalmia, polydactyly and cleft palate) indicative of trisomy 13 was not present for all our cases. This suggests that the clinical evaluation of a patient is not enough to make a diagnosis; even partial typical features, including or not the clinical triad, could implicate a possible Patau syndrome. In these conditions, it is mandatory to perform the cytogenetic analysis for accurate diagnosis and genetic counselling.

The mechanisms that cause this chromosomal abnormality are not completely known. The non-disjunction of autosomal chromosomes is one of the major causes of pregnancy loss in humans, being responsible for approximately 50% of spontaneous abortions before 15 weeks of gestation and approximately 50% of these are due to trisomies (3). Most aneuploidies result from disjunctional errors in maternal meiosis I, for which advanced maternal age could represent a risk factor. For 4 of our cases, maternal age was between 25 and 33 years and did not represent a risk for the appearance of trisomy 13. For case 4, maternal age is unknown. Although the mechanisms for the occurrence of trisomies are shared, there are some subtle variations of non-disjunction patterns among different chromosome subtypes consisting of diverse recombination patterns and varied meiotic stage errors. It seems

that there are specific non-disjunctional patterns that affect different chromosomal subsets, including the acrocentric chromosomes (4). For the majority of cases, the chromosomal disjunction errors in Patau's syndrome seem to have arisen mostly through maternal meiotic errors, similar to other trisomies; unusually, there are relatively equal numbers of meiosis I and II errors (5,6). As with other trisomies, for trisomy 13 failure to recombine is an important determining factor in the etiopathogeny of this chromosomal anomaly.

Abnormalities of chromosomes are classified as numerical and structural involving both autosomes and sex chromosomes.

Existing literature on chromosomal aberrations shows trisomy 21 to be the commonest, with its incidence 1:650-1:1000 live births (7). Trisomy 18 represents the second most common autosomal trisomy syndrome after trisomy 21. Because trisomy 18 is a relative common chromosomal cause of stillbirths, the frequency in total births would be higher than figure of 1 in 6000 (8). The best estimate of live births with trisomy 13 after accounting for prenatal diagnosis is approximately 1 in 10000 to 1 in 20000 (8). Turner syndrome is reported to occur in 1 in 2500 to 1 in 3000 live-born females, based on screening of newborn populations (8).

About 27% of the children reffered to our genetic department, selected cases, had chromosomal abnormalities, excluding the chromosomal variants. Trisomy 21 was the most autosomal trisomy observed. In our review trisomy 13 syndrome was the second most common numerical anomaly together with Turner syndrome, after trisomy 21, followed by trisomy 18 (Table 3). ❑

DIFFERENTIAL DIAGNOSIS

Holoprosencephaly-polydactyly syndrome (Pseudo-trisomy 13) (OMIM 264480) (9) is an autosomal recessive disorder associated with clinical features highly suggestive of trisomy 13, in the absence of an abnormal karyotype. This genetic entity is frequently related to consanguinity and is often misinterpreted as Patau syndrome in clinical practice.

Pallister-Hall syndrome (OMIM 146510) (9) is an autosomal dominant disorder comprising hypothalamic hamartoma, pituitary dysfunction, mesoaxial or postaxial polydactyly and visceral malformation (10).

Smith-Lemli-Opitz syndrome (OMIM 270400) (9) is an autosomal recessive multiple congenital malformation and mental retardation syndrome caused by the deficiency of 7-dehydrocholesterol reductase (11); the phenotype consists of prenatal onset growth deficiency, failure to thrive, microcephaly, postaxial polydactyly and Y-shaped 2,3 toe syndactyly (12).

Short rib-polydactyly syndrome is a descriptive category for a group of lethal skeletal dysplasias characterized by a hypoplastic thorax, short ribs, short limbs, polydactyly and visceral abnormalities, inherited in an autosomal recessive pattern. At least four types have been recognised (12).

McKusick-Kaufman syndrome (OMIM #236700) (9) and *Bardet-Biedl syndrome* (OMIM #209900) (9) have a phenotypic overlap particularly in infancy, all children should be re-evaluated for retinitis pigmentosa and other signs of Bardet-Biedl in later childhood (13). The phenotypic triad of anomalies consists of primary amenorrhea caused by complete lack of mullerian fusion with vaginal agenesis or mullerian aplasia, postaxial polydactyly and congenital heart malformation (14).

Microphtalmia with limb anomalies syndrome (OMIM %206920) (9) is an autosomal recessive disorder in consanguineous families characterised by unilateral/bilateral anophthalmia or microphthalmia, flat nasal bridge, cleft lip/palate, limb malformations (syndactyly, feet postaxial polydactyly), mental retardation.

These syndromes have some individual features in common with Patau syndrome but the

Number of malformed children reffered	**806**
Number of children karyotyped	**402**
Normal karyotypes	187
Abnormal karyotypes	215
Numerical anomalies	191
Down syndrome (trisomy 21)	177 (92,67%)*
Edwards syndrome (trisomy 18)	4 (2,09%)
Patau syndrome (trisomy 13)	**5 (2,61%)**
Turner syndrome	5 (2,61%)
Structural anomalies	24

TABLE 3. Summary of chromosomal analyses done in our department during 2007-2009, with number of abnormal cases and corresponding percentages for numerical anomalies

**(% from total numerical anomalies)*

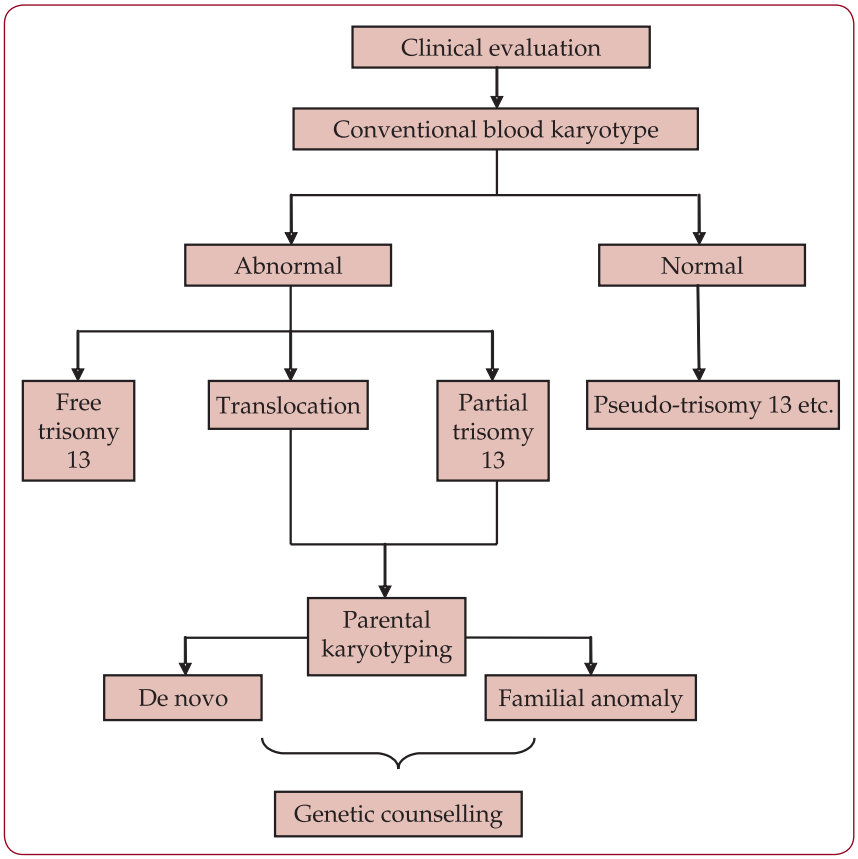

FIGURE 6. Practical steps for the evaluation of a patient suspected to have trisomy 13

cytogenetic diagnostic testing should allow these conditions to be excluded in most cases (Fig.6). ❑

TREATMENT AND CARE

There is no treatment or cure for trisomy 13. Early diagnosis of Patau syndrome is essential for proper management of the patients, including surveillance of some specific complications.

Survival

Mortality is high for newborns with trisomy 13; some patients will survive beyond the neonatal period, with a smaller number of cases surviving for many years. The evolution is correlated with several factors, including the severity of cardiac and cerebral malformations and of other multiple congenital anomalies (15).

Some authors have suggested that certain cytogenetic forms may be associated with longer survival (16). Others attributed this to the more aggressive management of individual cases with trisomy 13 (17).

Management issues

The Patau syndrome involves multiple abnormalities, many of which are not compatible with life. The type of treatment depends on the patient's individual condition.

Gastro-oesophageal reflux and feeding difficulties are almost invariable in trisomy 13. Aspiration during feeding or from reflux may cause cardiorespiratory arrest (12).

Cardiac defects occur in 80% of cases. For the congenital heart diseases common for trisomy 13, like atrial septal defect, ventricular septal defect, patent ductus arteriosus (PDA), the standard treatment is pharmacological intervention (for PDA) and palliative or corrective surgery (18).

Infants with trisomy 13 have significant involvement of central nervous system (CNS) and are at high risk of profound mental retardation. Holoprosencephaly and other forebrain developmental anomalies are common. Less commonly, these infants may have hypoplasia of the cerebellum, hydrocephalus and spinal dysraphism (19).

Eye problems are common in trisomy 13. The most frequent ocular findings of Patau syndrome are microphtalmia, coloboma of the iris and cilliary body and retinal dysplasia (20).

Many babies with trisomy 13 have extra fingers and toes (polydactyly) which could benefit of surgery. Cleft lip and cleft palate are present in 60-70% of cases and are also frequently surgically corrected (12).

Sometimes, infants with Patau syndrome can have scalp abnormalities (cutis aplasia) which resemble ulcers (12).

Other uncommonly associated manifestations include: renal and genitalia abnormalities, ectrodactyly (21), hypoplastic pelvis, single umbilical artery, inguinal hernia, umbilical hernia etc. (1) (16)

In conclusion, considering the different aspects of the evolution of a patient with trisomy 13 and possible complications, it is necessary a multidisciplinary approach for the management and treatment of such cases.

Inheritance and genetic counselling

Genetic counselling is based on clinical evaluation, exploring family history and cytogenetic analysis; it is a complex procedure due to the different chromosomal aberrations. The work-up of a patient suspected of chromosomal anomaly starts with a detailed dysmorphology examination. Because we need to have a preventive approach family history is very important to identify other family members that might be at risk, although sometimes in practice is not possible to do a complete investigation due to the incompliance of the family.

Cytogenetic analysis is crucial for every newborn with high risk of chromosomal abnormality. If an aneuploidy of chromosome 13 is found, the recurrence risk depends on the genetic variant of the anomaly. For the free trisomy 13 variant the recurrence risk is low. In this type of situation, the parents karyotype is not necessary because most cases of this kind are isolated occurrences. For the other two variants (Robertsonian translocations and partial trisomy 13), the risk of recurrence is high and parents karyotype must be performed. Also, FISH (Fluorescence in Situ Hybridization) studies could be usually used to describe more accurately some chromosomal anomalies. Prenatal cytogenetic analysis from CVS (chorionic villus sampling) or amniotic fluid can provide diagnosis and help the family to avoid recurrence. Echographic evaluation of malformated fetuses is important for prenatal diagnosis and counselling. Cytogenetic analysis could identify a precise prenatal diagnosis and could characterise a malformative syndrome. Recurrence risks for future pregnancies must be addressed in all cases, whether aneuploidy or structural rearrangements are involved.

The psychological support offered to the parents may contribute positively to the survival of patients with less severe phenotype and to the maintenance of family-child relationship. Early intervention programs will be very important for the small number of children with Patau syndrome that will survive through the first months of life. ❑

CONCLUSION

1. This study demonstrates the importance of cytogenetic evaluation in patients who have clinical features resembling Patau syndrome.
2. The result of chromosomal analysis is mandatory for genetic counselling because recognition of parents with chromosomal rearrangements is very important, as the risk of recurrence is high for some cases. For these cases, prenatal cytogenetic testing is necessary to prevent the birth of another child with this syndrome
3. The precise delineation of Patau syndrome is only possible using clinical examination and cytogenetic tools.
4. Management and treatment of patients with trisomy 13 demands a multidisciplinary approach.

FUNDING

This work was supported by Romanian Ministry of Health's National Programs, Objective 3.

References

1. **Gorlin RJ, Cohen Jr. MM, Hennekam RCM** – *Syndromes of the head and neck.* 4th Edition. s.l.: Oxford Univ. Press, 2001
2. www.cdc.gov. [Online] [Cited: September 19, 2010.]
3. **Hassold T, Chen N, Funkhouser J et al** – A cytogenetic study of 1000 spontaneous abortions. *Ann Hum Genet* 1980; 44:151-178
4. **Nicolaidis P, Petersen MB** – Origin and mechanisms of non-disjunction in human autosomal trisomies. *Hum Reprod* 1998; Vol. 13, 2:313-319
5. **Bugge M, Collins A, Hertz JM et al** – Non-disjunction of chromosome 13. *Hum Molec Genet* 2007; Vol. 16, 16
6. **Hall HE, Chan ER, Collins A et al** – The origin of trisomy 13. *Am J Med Genet A* 2007; Vol. 143A, 19:2242-2248
7. **Hassold TA, Sherman S** – Down syndrome:Genetic recombination and origin of the extra chromosome 21. 2000; 57:95-100
8. **Suzanne B.Cassidy, Judith E Allanson –** *Management of genetic syndromes.* New Jersey: John Wiley&Sons, 2005. pp. 555-558.
9. www.ncbi.nlm.nih.gov/omim. [Online] [Cited: August 16, 2010.]
10. **Biesecker LG, Abbott M, Allen J et al** – Report from the workshop on Pallister-Hall syndrome and related phenotypes. *Am J Med Genet* 1996; 65:76-81
11. **Tint GS, Irons M, Elias E et al** – Defective cholesterol biosythesis associated with the Smith-Lemli-Opitz syndrome. *New Eng J Med* 1994; 330:107-113
12. **Helen V Firth, Jane A Hurst** – *Oxford Desk Reference Clinical Genetics.* s.l.: Oxford University Press, 2005. p. 76
13. **David A, Bitoun P, Lacombe D et al** – Hydrometrocolpos and polydactyly: a common neonatal presentation of Bardet-Biedl and McKusick-Kaufman syndromes. *J Med Genet* 1999, 36:599-603
14. **Slavotinek AM, Dutra A, Kpodzo D et al** – A female with complete lack of mullerian fusion, postaxial polydactyly and tetralogy of Fallot: genetic heteregoneity of McKusick-Kaufman syndrome or a unique syndrome? *Am J Med Genet* 2004; 129a:69-72
15. **Rasmussen SA, Lee-Yang CW, Quanhe Y et al** – Population-based analyses of mortality in trisomy 13 and trisomy 18. *Pediatrics* 2003; Vol. 111:4
16. **Hodes ME, Cole J, Palmer CG, Reed T** – Clinical experience with trisomies 18 and 13. *J Med Genet* 1978; 15:48-60
17. **Goldstein H, Nielsen KG** – Rates and survival of individuals with trisomy 13 and 18. Data from a 10-year period in Denmark. *Clin Genet* 1988; 34:366-372
18. **Kaneko Y, Kobayashi J, Yamamoto Y et al** – Intensive cardiac management in patients with trisomy 13 or trisomy 18. *Am J Med Genet A* 2008; Vol. 146A, 11:1372-1380
19. **Maria Bernard L** – *Current management of child neurology.* 4th Edition. s.l.: People's Medical Publishing House, 2009. p. 371
20. **Bunting R, Leitch J** – Buphthalmos in trisomy 13. *Eye* 2005; 19:487-488
21. **Urioste M et al** – Ectrodactyly in trisomy 13 syndrome. *Am J Med Genet* 1994; 53:390-392