FANCONI ANEMIA WITH CLEFT PALATE

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FANCONI ANEMIA WITH CLEFT PALATE (Abstract): Fanconi anemia (FA) is a rare plurimalformative syndrome (1/350,000 newborns) presenting a large phenotypic heterogeneity, chromosomal instability and autosomal recessive inheritance (OMIM 227650). Case presentation: Male patient followed in the genetics service since infancy, till death. The child was referred for multiple congenital anomalies: bilateral aplasia of the radius and thumb, left kidney agenesis, cardiac malformation cleft palate, bilateral cryptorchidism, ear anomalies, which were associated, in time, with facial hyperpigmentation, anomalies of dental eruption, nasal septum deviation, and lumbar scoliosis. By the age of 10 years, he develop progressive pancytopenia, aplastic anemia. The diagnosis was completed by medulogram, immunogram, and karyotype. Treatment was primarily hematologic with substitution products, immunosuppressive, marrow stimulants, antibiotic therapy. Death occurred at age of 16 by infection and pulmonary hemorrhage occurred in severe pancytopenia. Conclusions: It is presented a rare case of Fanconi anemia customized by the clinical association with cleft palate and instructive clinical and evolutionary complexity. Keywords: FANCONI ANEMIA, CLEFT PALATE, CHROMOSOMAL INSTABILITY.

Fanconi anemia (OMIM 227650) is a rare plurimalformative syndrome presenting a large phenotypic heterogeneity, chromosomal instability and autosomal recessive inheritance. Recent determination of the carrier frequency gave an estimate of more than 1/200, with an expected prevalence at birth of at least 1/160,000. In certain populations, the carrier frequency is much higher, due to founder mutations. Until now, more than 2000 cases have been reported in the literature (1).

CASE PRESENTATION
A 16 year old boy, the first child in family, born at term, birth weight 2900 g; APGAR score 8/9. The parents are young and healthy and they are non-related. From past medical history: cleft palate (DP) operated at 1 year and; at 3 years old he was operated for cryptorchidism (orchiopexy). The boy was in evidence of Genetics Department from birth with plurimalformative syndrome (cleft palate, anomalies in size and shape of upper limbs).

Physical examination at 16 years old reveals: growth retardation, pallor; on the face presents ephelides and hyperpigmentation. Craniofacial dysmorphism (fig. 1): microcephaly, long face, microphthalmia,
epicanthus, anteverted ears, sharp nose, long neck. Oral cavity: palate with keloid scar after surgery. Upper limbs: bilateral, symmetrical shortening of the forearm (shortened to half of the normal size), forearms were a single long bone with bilateral thumb agenesis; lumbar scoliosis (fig. 2).

**Fig. 1.** Craniofacial dysmorphism, dental anomalies, keloid scar after surgery correction of cleft palate

**Fig. 2.** Size and shape anomalies of the upper limbs

**Laboratory investigations** showed: count blood cells (CBC): severe tricyto-penia; elevated levels of urea, creatinine and urine density. Bone marrow aspirate showed global marrow hypoplasia, marrow with fat tissue. Immuno-phenotyping revealed low number of NK cells; very low levels of lymphocytes B. In absolute value: lymphopenia with a marked decrease in lymphocyte B accompanied by a moderate decrease in NK cells. CD4/CD8 ratio is at the lower limit of normal. X-Ray: bilateral agenesis of the radius; lumbar scoliosis. Abdominal ultrasound: moderate hepatomegaly, absent left kidney and right kidney is hypoplastic and misaligned. Computer tomography (CT): absence of left kidney and pelvian position of the right kidney; dextroconvex lumbar scoliosis.

**Interdisciplinary checkups:** cardiology exam including EKG: minor right arterial block. ENT exam: nasal septum deviation. Psychological evaluation: IQ 90.

**Genetic investigations:** We performed karyotype from peripheral blood: it was normal: 46, XY, but does not excluded the existence of chromosome breakages. Bone marrow karyotype showed a fragile site on the long arm of chromosome 12 band q14 (fig. 3).

**The differential diagnosis** include: the VATER/VACTERL association, Holt-Oram syndrome and TAR syndrome (thrombocytopenia and radial agenesis) mainly due to the radial abnormalities. Other conditions to be considered include the Blackfan-Diamond anemia (especially because of the hematological features), and other chromosomal instability syndromes such as the Bloom syndrome and the ataxia-telangiectasia syndrome (2).

**Treatment** was as follows: substitution: red cell transfusions; bone marrow stimula-
tion: androgens, growth factors G-MSC (Neopogen); immunosuppressant: Prednisone, symptomatic: antibiotics, vitamins, Calcium, Magnesium, Aspacardin. Marrow transplant was not performed because no compatible donors.

Evolution: at the age of 16 ½ years dies due to sepsis with multiple organ dysfunctions leading to severe pulmonary hemorrhage

DISCUSSION

Fanconi anemia, ataxia - telangiectasia and Bloom syndrome are hereditary disease resulting from mutations in genes that contribute to genome stability. Genomic instability promotes chromosomal breaks and rearrangements which is evidentiable by light microscopy examination of metaphase cells (3, 4, 5).

Today are identified 16 FA or FA-like genes: FANCA, FANCB, FANCC, FANCD1, FANCD2, FANCA, FANCF, FANCG, FANCA, FANCI, FANCL, FANCM, FANCN, FANCP and RAD51C, XPF. Proteins codified by FA genes play a role in cellular response to oxidative stress, in cell cycle regulation, in DNA repair and chromosomal stability in tumor suppression. Majority patients have mutations in group A (60%), C (15%) or G (10%) of rest of 15% belongs to other subtypes (6, 7).

Most persons with Fanconi anemia develop malignancy, usually acute myeloid leukemia; 90% of patients develop bone marrow failure by the age of 40 years.

In 1927 Guido Fanconi described a family with three boys who had various birth defects and who subsequently developed pancytopenia (8). The syndrome is characterized by developmental defects, bone marrow failure and increased risk of cancer.

It is autosomal recessive inheritance in 99% of cases. Only FANCB gene is located on chromosome X such that its transmission will be recessive X linked (9).

The frequency in the general population is 1/350,000 births. FA occurs in all ethnic groups, but with a higher frequency (1/100 individuals) in Ashkenazi Jews and African population from South Africa (10, 11).
CONCLUSIONS
Fanconi anemia is a very heterogeneous condition clinically and patients can have a wide variety of abnormalities. Particularity of this presentation consists in associating with cleft palate, rarely described in the literature. The clinicians must recognize the considerable overlap of the FA phenotype with other malformation syndromes, and the need for applying a specific laboratory diagnostic test.

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IN VITRO EVALUATION OF ANTIBACTERIAL EFFICACY OF PINEAPPLE EXTRACT (BROMELAIN) ON PERIODONTAL PATHOGENS

Periodontitis represents an inflammatory disease resulting in the destruction of periodontal tissues. Various treatment modalities (mechanical and surgical therapy) have been tried. Antimicrobial agents have been used as a monotherapy and as an adjunct with mechanical debridement. As antibacterial agents have been used different plant extracts. Pineapple extract (Bromelian) is one such agent. The aim of the study was to assess the antibacterial efficacy of Bromelain on aerobic and anaerobic periodontal microorganisms. Minimum inhibitory concentration (MIC) of Bromelain was tested on isolated strains of Streptococcus mutans, Enterococcus fæcalis, Aggregatibacter actinomycetemcomitans (Aa), and Porphyromonas gingivalis (Pg) using serial dilution broth method. The results of the study showed that S. mutans showed sensitivity at the lowest concentration of 2 mg/ml as compared to E fæcalis (31.25 mg/ml) while P gingivalis showed sensitivity at the lowest concentration of 4.15 mg/ml as compared to Aggregatibacter actinomycetemcomitans (16.6 mg/ml). In conclusion Bromelain exerts an antibacterial effect against potent periodontal pathogens; hence, it may be used as an antibacterial agent. To validate this result further trial has to be conducted. (Praveen NC, Rajesh A, Madan M, Chaurasia VR, Hiremath NV, Sharma AM. In vitro Evaluation of Antibacterial Efficacy of Pineapple Extract (Bromelain) on Periodontal Pathogens. J Int Oral Health, 2014; 6 (5) : 96-98).

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