Fanconi's anemia - Retrospective study over a period of 37 years

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1. Introduction

Fanconi anemia (FA) is a rare disease, with an estimated frequency of 1 to 5 per 1,000,000 births, which may increase in some ethnic group (like Ashkenazi Jewish and Gypsy). It's an autosomal recessive disease that may have an X-linked transmission. Patients with FA may have congenital malformations, bone marrow failure, hypersensitivity to clastogenic agents, chromosomal fragility, and increased susceptibility to oncological diseases. Due to the great complexity of this pathology, the first approach to diagnosis consists of the detection of chromosomal aberrations (breaks, structural rearrangements, rings) in peripheral blood cells in culture with clastogenic agent such as diepoxybutane (DEB) or mitomycin C (MMC).

2. Objective

We intend to present the results of chromosome instability studies induced by DEB and MMC performed in our institution.

3. Methods

The analysis of a retrospective series of 37 years (1980-2017) of 274 samples sent to the cytogenetic laboratory with suspicion of FA and 28 samples of relatives of patients with FA were performed. In total, 265 samples of peripheral blood (PB), 3 of skin biopsy, 3 of amniotic fluid, 1 of cord blood and 2 of marrow blood were analyzed (see **Fig. 1**).

The samples were processed according to the established protocol for the chromosomal analysis of fracture associated diseases, including cell culture with MMC and / or DED stimulation for each biological product, followed by microscopic analysis with determination of the DEB-induced chromosomal instability and / or MMC according to the protocol established by the International Fanconi Anemia Registry (IFAR).

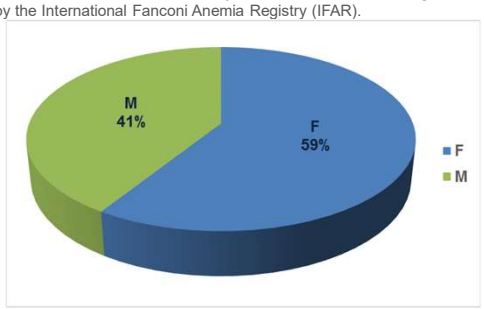

Fig. 2: Informative graph of the prevalence of female subjects (F) vs. male (M) with FA.

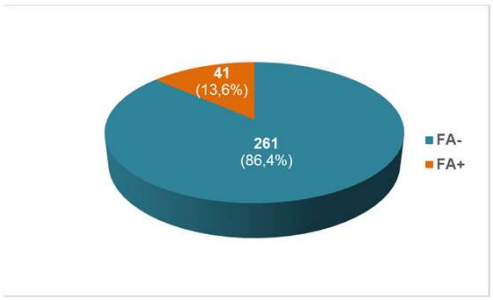

Fig. 3: Graph with the number of patients identified with FA.

4. Results

- The mean age at diagnosis of FA patients was 7 years, with a slight predominance of females (**Fig. 2**).
- In the 274 analyzed samples, 39 cases with FA were identified. (**Fig. 3**)
- In the cytogenetic studies of relatives with FA, 2 positive cases were identified.
- Therefore, we can say that we evaluate 302 samples in which we found 41 new cases of FA.
- In 6 samples of suspected FA, were observed abnormal karyotypes (**Table 1**).

5. Conclusion

- In this study, 41 new cases were identified with FA, mainly from the Lisbon and Tagus Valley, some specific cases from the Autonomous Region of Azores, central region of Portugal and from the Portuguese-speaking African countries (PALOP).
- This study evidences that most cases are underdiagnosed due to phenotypic overlap with other syndromes. On the other hand this overlap, justifies the very high percentage of negative FA obtained.
- Within the FA group, there are samples that, despite presenting a phenotype similar to that of a patient with FA, present an abnormal karyotype (**Tab.1**). For this reason and as a form of primary screening, a constitutional karyotype should be considered simultaneously with the Fanconi Anemia research.
- These results do not allow to estimate a frequency of patients with FA in Portugal, since it does not include individuals from all Portuguese regions, on the other hand two individuals of PALOP origin are included.
- It would be interesting to carry out Next generation sequencing on the Fanconi positive samples in order to obtain in a single assay the analysis of the various genes involved in the pathology thus identifying the genetic change causing the disease.

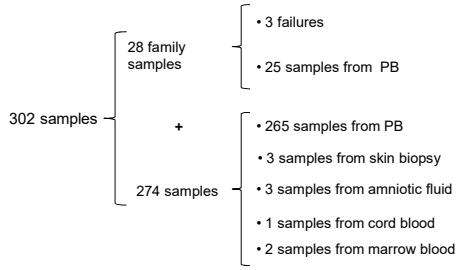

Fig. 1: Explanatory scheme of the samples analyzed over 37 years (1980 to 2017).

Tab. 1: Abnormal karyotypes obtained from the 302 samples analysed with suspicion of FA.

Sample Nº	Clinical Information	Overlap with FA phenotype	FA	Karyotype	Phenotype vs karyotype (Bibliographic data)
I	•Bilateral agenesis of the radio	+	-	mos47,XY,+7[3]/ 46,XY[47]	short[6]
	•Prominence of frontal bosses	-			Clinodactyly[6]
	•Dysmorphic hands	+			Body asymmetry[6]
	•No blood count changes	-			Triangular Facies[6]
II	•Psycho-motor development delay	+	-	46,XY,dup(2)(p23.1p24.3).ish dup(2)(wcp2+)	Psycho-motor Development Delay[7]
	• Weight and height less than P5 since 6 months	+			Microcephaly[7]
	•Low thumb implantation	+			Prominent forehead[7]
	•Other small dysmorphic	+			Facial dysmorphisms[7]
III	• Malformations of the upper limbs	+	-	47,XX,+mar[2]/ 46,XX[28]	-
IV	•Thin thrombocytopenia + macrocytosis	+	-	46,X,i(X)(p10)[11]/46,XX[39]	Pancytopenia with marked thrombocytopenia[8]
	• ↑ Fetal Hb	+			
	• Focomelia	+			Hematologic diseases[8]
	•LCA (Congenital Amaurose Leber)	-			Apnea[8]
	•Poor weight evolution	+			Hypotonia[8]
	•Short	+			Growth retardation[8]
V	•Low set ears	+	-	47,XY,+mar[6]/ 46,XY[44]	-
	•Short	+			
	•*Coffee au lait spots*	+			
VI	•Growth retardation	+	-	46,XY,t(7;20)(p15;p13)[30]	In the short arm of cr. 7 in p15 is an *ETV6* partner gene, the *ANLN*, which may induce a hematological change in some way. On the other hand, on chromosome 20 in p13 there are cell cycle regulator genes that together with *ANLN* may somehow induce marrow failure.[9,10]
	•Single kidney to the left	+			
	•Medullary Failure	+			

6. Bibliography

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