A tribute to Fanconi: 'clinical acumen still counts'

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"*It is the doctor's privilege to pursue an occupation which is also his favourite pastime*" Guido Fanconi (1892-1979): 'a jack of all trades'[1]

Fanconi anemia (FA), a predominantly autosomal recessive disease, most frequently presents with bone marrow failure (BMF). Hematologic manifestations such as BMF, clonal evolution to myelodysplastic syndrome and acute myeloid leukemia,[2] predominate in FA and can be the presenting feature or the most significant cause of morbidity and mortality.[3] However, other manifestations in FA such as solid tumors, especially squamous cell carcinomas, as well as disorders of other organ/systems including renal, gastro-intestinal, cardiac, endocrine and musculo-skeletal systems need specialist input and coordinated management plans, as advances in treatments, such as hematopoietic stem cell transplantation in FA,[4] become more successful and overall survival improves.

As with many 'multigenic' diseases, phenotypic and genotypic correlation needs to be better understood in order to predict the natural history and outcome of the disease. Chromosomal breakage analysis as a diagnostic tool for FA, is widely used but genotypic characterization is progressing rapidly and is much needed.

In this issue of *Haematologica*, Altintas *et al.* report on a large National Cancer Institute retrospective cohort of 203 patients, with nearly 50% harboring *FANCA* mutations.[5] Genetic characterization of FA is based on whether there is an upstream (80%), ID complex (9-11%) or downstream (5-9%) defect and whether this results in a "null" or "hypomorphic" variant. Interestingly, the data collected by Altintas *et al.* were divided into those from patients 'in the field' (72%) (remote data collection through questionnaires) and patients in a clinic cohort (28%) (review at the National Institutes of Health clinical center) to associate patterns with phenotypic correlation and presentation. This demarcation into two cohorts was arbitrary and could have introduced ascertainment and assessment biases, especially in FA patients with subtle physical features, but paradoxically underscores the importance and necessity for more systematic and detailed assessment and was able to correlate genotype to phenotypic abnormalities in the clinical cohort.

Although the findings are largely confirmatory,[6] the report contains a lot of information from pioneers in the field of FA and updates the current knowledge regarding how FA genotype affects patients' phenotypes including BMF, solid tumor development, pregnancy, and physical abnormalities.

A few significant observations in this large cohort study have practical relevance and underpin the value of tertiary/specialist centers with expertise in evaluation, screening, and future management strategies, including timing of hematopoietic stem cell transplant and exciting novel therapies.

All patients evaluated in the National Institutes of Health clinical center had physical abnormalities and interestingly only 5% (3/57) did not have pathogenic variants in the FA/BRCA DNA repair pathway, as compared to 22% in the field cohort. The counter argument to this is that patients with subtle features who remain undiagnosed into adulthood, are detected with additional anomalies and features of multi-system FA disease when reviewed in specialist centers.[6]

Although slightly less than a century has passed since the first clinical description of FA by Dr Guido Fanconi,[7] the genomic revolution has expanded the repertoire of pathogenic mutations from 15 known FA genes in 2010[3] to at least 22 genes in the FA/BRCA DNA repair pathway in 2022. Although conventionally FA patients with mutations in the upstream complex have fewer physical abnormalities and a milder phenotype compared to those with mutations in the ID complex, upon assessment at a tertiary center subtle abnormalities, not included in the VACTERL-H (Vertebral, Anal, Cardiac, Tracheo-esophageal fistula, Esophageal/duodenal atresia, Renal, Limb, Hydrocephalus)/PHENOS (Pigmentation, small Head, small Eyes, Neurologic, Otologic, Short stature) constellations of anomalies, were evident on physical assessment, especially in *FANCA/FANCC* patients. This clearly signifies the added value of comprehensive evaluation in a specialist center with multidisciplinary clinical, genetic and biological expertise, at least as a 'one-stop' clinic, with subsequent remote monitoring in the era of telemedicine, a practice strengthened by the COVID-19 pandemic.

BMF was present in 86% of the cohort, with an increased

risk of myelodysplastic syndrome/acute myeloid leukemia in *FANCC* cases. Clinical features and other tools to predict the development of BMF and clonal evolution are extremely helpful and aid in planning pre-emptive hematopoietic stem cell transplantation. The ability to predict early BMF in FA patients with PHENOS features, which interestingly overlaps with the previously reported congenital abnormality score (CABS) and the well-described association with absent radii, is valuable. Chromosomal abnormalities and also markers of clonal hematopoiesis, and their role in prediction models for BMF and development of myelodysplastic syndrome/acute myeloid leukemia in FA will become refined and redefined in the near future.

The risk of development of solid cancers and metabolic/endocrine (mainly hypothyroidism) abnormalities are well described in FA and can be a result of the disease and/or therapy, especially after hematopoietic stem cell transplantation. These risks are particularly important to include in a systematic algorithm for monitoring.[8,9]

Some of the novel findings and interesting observations, which need further validation and biological explanation, are: (i) an increased risk of solid tumors in patients with *FANCA* variants involving exon 17-20, which is essential for nuclear localization; fertility preservation and ability to conceive for female patients with a c.3624C>T synonymous variant in the *FANCA* gene; (ii) clinical heterogeneity between FA siblings with identical variants; and (iii) lack of 'hotspot' mutations in *FANCA* compared to *FANCD2*.

The age at diagnosis and at registration of the FA patients in the study by Altinas *et al.* was 5.4 and 11.2 years, respectively, with the upper limit close to 60 years. No additional correlation between age at presentation and physical features was presented. This is critically important to evaluate in future studies and useful for hematologists caring for adults, who usually deal with non-syndromic diseases, as most of the inherited BMF syndromes, including FA, which present in adulthood manifest with subtle physical features, less cytopenia and more solid cancers or lung/liver fibrosis, this last feature in the context of telemeropathies. It is possible, although only a speculation, that some of the cases of FA diagnosed in adulthood could be due to mutations in the upstream complex in view of the milder phenotype reported for the *FANCA* genotype in children and adolescents. Phenotype-genotype analyses will undoubtedly continue to develop and can help in predicting the natural history and multi-system manifestations of FA, including prognosis for counseling, and risk-stratified management strategies. These analyses have yet to achieve their maximum potential and, therefore, utility. The field and clinic cohort modeling that the authors developed in their study, as well as the description of the PHENOS phenotype, are steps in that direction. Mutational diversity as well as inconsistent phenotypes do. however limit their utility to a certain extent.

Large phenotype-genotype correlations in FA will help us to understand the natural history and biology of the disease and thereby advance the field of therapeutics which is evolving to correct BMF (gene therapy and gene editing),[10,11] halt the progression of BMF (modulate endogenous aldehyde metabolites or microbiome)[12] and restore stem cells (eltrombopag) while simultaneously using novel strategies to prevent/treat solid cancers in FA.

Disclosures

No conflicts of interest to disclose.

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