Failure or delay in diagnosing Fanconi anemia - a well-defined genetic disorder

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To the Editor,

Fanconi anemia (FA), first described in 1927, is one of the inherited bone marrow failure syndromes (IBMFSs), a heterogeneous group of genetic disorders characterized by marrow failure usually in association with somatic abnormalities and increased risk of malignancy[1]. Patients with FA may have one or more developmental abnormalities (skin, skeletal, genitourinary, gastrointestinal, and neurological anomalies)[2]. Affected individuals generally develop marrow dysfunction that can involve all or a single cell lineage, myelodysplastic syndrome (MDS), or acute myeloid leukemia (AML). Most patients have macrocytosis in infancy or childhood[2]. Nonhematologic malignancies in FA patients are solid tumors, particularly of the head and neck, skin, gastrointestinal tract, and genital tract[3]. Fifteen genetic subtypes have been distinguished: FA-A, -B, -C, -D1, -D2, -E, -F, -G, -I, -J, -L, -M, -N, -O, and –P. The majority of patients (85%) belong to the subtypes A (60%), C (10–15%), or G (10%), while a minority (15%) are distributed over the remaining 12 subtypes. The mode of inheritance for all subtypes is autosomal recessive, except for FA-B, which is X-linked. For all genetic subtypes, disease genes have been identified[4].

As understood from the condensed summary above, FA is a well-defined genetic disorder, with clinically recognizable features. Despite the distinguishable features and many developments at all points of the disease progression, cases of delayed diagnosis, or more correctly, "overlooked cases", still occur. This is seen similarly in those populations in which the disorder was originally defined and the majority of related molecular developments were observed. Examples of this speculation include the remarkable accounts of cases presented in FA Family Newsletters, the official publication of the Fanconi Anemia Research Fund[5,6]. The same subject has also been addressed in a recent issue of a remarkable journal via a quiz case[7]. From the physical and laboratory findings, it is clear that the patient suffers from FA; unfortunately, she was not diagnosed appropriately until the age of 16. The reasons for the failure or delay in diagnosis of FA even in cases with apparent features should be meticulously considered, since this could lead to a missed opportunity for bone marrow transplantation (BMT) and the development of cancer or even death due to complications developing during the cancer treatment. With this letter, we share our viewpoints on this subject, including our thoughts regarding the general knowledge level of clinicians about FA and the factors that negatively affect their awareness of this disorder.

Why do FA cases continue to go unrecognized? Possible contributing factors are presented hereunder:

1-The erroneous assumption that all cases will present with the classical clinical and laboratory findings

Classical textbooks suggest that all FA patients present with the typical findings. In these books, a case with the classical findings is presented first, and then all the abnormalities that might be observed in FA cases are explained in detail[8]. This presentation draws the reader's attention to the pathological findings. However, at least 25% of individuals with FA have no physical abnormalities[2]. FA patients with normal hematological findings are also reported[2]. Thus, the absence of physical abnormalities or marrow failure does not exclude the diagnosis. However, this significant detail is almost ignored under the weighty information presented about the abnormalities associated with FA. The possibility of such cases is stated only in a sentence, and no images are presented. More attention to these patients and to others' having only subtle abnormalities, together with visual materials, might be given

in the related chapters. In addition, reviews, similar to the comprehensive review by Shimamura et al.[9], to reveal the number of FA patients with normal features among the cases published so far (including those non-registered in the current FA registries) might be prepared by the IBMFSs study groups. The titles for these reviews might be organized so as to emphasize the occurrence of patients with normal laboratory and clinical findings. In this way, the notion that patients may present with even completely normal clinical and laboratory features could be created and/or strengthened.

2-The fact that a large amount of effort related to FA has been directed to the disorder itself rather than to the affected cases

Nowadays, scientists work primarily at molecular research laboratories with the patient-derived cells[10]. Researchers conduct molecular studies to unravel the processes behind the disease. To obtain the cells that will be molecularly investigated and thereby make possible the presentation of the scientific truths, however, the cases of FA should be recognized first, since they themselves are the cell source. The greater the number of cases recognized, the greater the light that may be shed upon the disease. In this regard, the first to be aware of the cases are clinicians. Thus, more effort related to FA might be directed to the clinicians, with the primary aim to improve their recognition of the cases, i.e., the disorder with all its presentations, and to support the research scientists by more valid clinical data.

3-The general priority assigned by medical journals to molecular research papers

Today, clinical case reports are considered to be almost "simpler" and "less scientific" compared to molecular research articles. As a result, molecular research articles are accorded priority in most medical journals. As can be accepted, cases are generally required in order to carry out a scientific study and compose a scientific paper. An accumulation of cases would lead to 'case series' and 'reviews', and thereafter, a comparative assessment of reviews would shed light on specific diseases. Thus, appropriate emphasis on clinically important case reports in medical journals of all levels might be useful.

4-The tendency to not publish patient photographs to protect patient privacy

In the published literature, there is an increasing bias not to identify patients. In accordance, patients and/or their guardians do not give consent for publication of their pictures. However, diseases, particularly those recognizable from the phenotypical features, cannot be fully comprehended from description alone. As accepted, while it is difficult to recognize the distinguishable features of the syndromes by reading, it is quite easy by observation. Recognizing that a clinician cannot possibly encounter cases representing every kind of disorder, and further, that critical disorders that are confused cannot be placed comparatively in classical textbooks, the value of the case reports becomes evident. Providing the readers an opportunity, if available, to see clearly the patient's phenotypic appearance in these articles would be helpful. Thus, patient photographs are of utmost importance. If the implications for future FA patients are clearly explained to the patient and/or guardian, there may be less objection to the publication of their photographs, with some perhaps even taking pride in their contribution to science and assistance to their fellow man.

In accordance with these views, a search of the published medical literature (PubMed) over the last five years using the keyword "Fanconi anemia" revealed 873 articles. Of those, only 82 (9.4%) are case reports. An assessment of the case reports revealed only four reports with informative photographs. Thus, among the related articles published in the last five years, the percentage of reports including an informative image of the patient is 0.5% (4/873), and among the case reports, this rate is 4.9% (4/82). Only regional images, at best, were included in the remaining articles. Such pictures, in our opinion, might be satisfactory for a health professional familiar with FA; however, they would be insufficient for a beginner to recognize the FA phenotype. Because visual perception, a function of our eyes and brain, is "holistic", it makes us see images as a whole rather than in parts. Only after our eyes see images and our brain recognizes them, can the images be broken down into their meaningful visual elements[11].

Another probable explanation for the diagnostic difficulties in FA in some countries, such as in

Turkey, might be the unavailability of molecular confirmation for cases with a clinical diagnosis. In the event that the chromosomal breakage test is not available and/or is inconclusive due to possible somatic mosaicism, the diagnosis is compromised, particularly if the patient has no overt abnormalities. In such patients, a definite diagnosis based on a molecular confirmation cannot be established. As a result, the compliance between the family and the treating physician might be interrupted, and the mother might give birth to new afflicted babies. International collaboration to provide free genetic analysis for such cases might resolve this issue.

In conclusion, though FA was described nearly a century ago, and striking improvements have been achieved with regard to many aspects of the disease, there are still difficulties in recognizing FA. This is a subject of concern for everyone involved with FA. With this letter, we aimed to share our uneasiness in this regard and to present our perspectives, together with some possible suggestions for resolving the current oversights. In our opinion, the cases should be the focus of the current suggestions towards a resolution. We believe that cases are essential elements to science, just as cells are the building stones of an organism. Every further effort to recognize cases of FA may lead to a small decrease in the number of overlooked FA cases, and also contribute to the collection of valid clinical data for research.

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