


## CASE REPORT

# Scapula alata as presenting symptom of Fanconi anemia: A case for serendipity

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## Abstract

Fanconi anemia is a recessive genetic disorder with a wide range of presenting symptoms, from multiple congenital defects to exclusively (pan) cytopenia. Scapula alata may be a rare symptom of FA.

## KEY WORDS

Fanconi anemia, scapula alata

## 1 | INTRODUCTION

Fanconi anemia is a rare disease leading to pancytopenia and a dramatically reduced life expectancy. We discuss a novel presentation in a 7-year-old girl, with scapula alata, retrospectively congenital, and her 5-year-old brother, subsequently diagnosed. The diagnosis was made following an unexpected course.

Fanconi anemia (FA), the most common form of the aplastic anemias, is a recessive genetic disorder with an estimated carriership of 1:300 and disease prevalence of 4–7:1 000 000.<sup>1,2</sup> FA is characterized by genome instability, bone marrow failure, and cancer predisposition.<sup>3</sup> Several studies showed a significant humoral and cellular immune dysfunction in patients with FA.<sup>3</sup> As a result of the high variety in presentation, the diagnosis of FA will often be confirmed after the pancytopenia appears. The most frequently associated congenital malformations are those of the skeletal system, mainly radius and thumb. We report a rare abnormality in a Fanconi anemia patient: scapula alata. A scapula alata was also described in one other case.<sup>4</sup>

## 2 | PRESENTATION

Patient A, a 7-year-old-girl was, at the request of her parents, referred by her general practitioner to our outpatient center, with a scapula alata. Both of her parents and her younger brother are of normal intelligence and normal phenotype. Her medical history shows an extensive evaluation in an academic hospital within the first week after birth, following the discovery of a duodenal web, for which she was operated. She also had other anomalies: She was microcephalic, had a clubbed foot, webbed neck, microphthalmus, and epicanthus. A clinical geneticist examined her and laboratory investigations revealed a normal 46 XX karyogram. There were no signs of pancytopenia in her blood count. No specific genetic diagnosis was made.

She developed normally until the age of 2 years. She was then referred to an ENT-specialist because her parents and kindergarten teacher suspected hearing problems. A right-sided conduction deficit was noted, and she received a hearing aid.

At her presentation at our outpatient clinic, it became apparent that her clearly asymmetrical shoulder height and form had not previously been noted by her parents, yet in retrospect was clearly seen in old photographs. The patient had no complaints of her shoulder. A general physical examination revealed, besides the already described anomalies, a few pretibial hematomas and a left-sided scapula alata. She was referred to both an orthopedic surgeon and a pediatric neurologist. No other abnormalities of the shoulders, joints, muscles, or nerves were found, and the diagnosis of congenital scapula alata was therefore most likely. However, at presentation at the neurologist, a large unexplained hematoma was noted on her left elbow. She was referred back to the pediatrician, where laboratory investigations were performed: Hb 6.9 (7.1-9.6) mmol/L, Ht 0.31 (0.32-0.43) L/L, MCV 103 (75-95) fL, thrombocytes  $27 (150-400) \times 10^9$ , leukocytes  $3.0 (4.5-14.5) \times 10^9$ , eosinophils  $0.0 (<0.4) \times 10^9$ , basophils  $0.0 (<0.2) \times 10^9$ , granulocytes  $0.9 (1.5-9.0) \times 10^9$ , lymphocytes  $1.9 (1.5-4.6) \times 10^9$ , monocytes  $0.4 (0.2-0.8) \times 10^9$ . No blasts were seen in the peripheral blood, the presence of which would indicate leukemia. The thrombocytopenia and neutropenia were reason to repeat the laboratory investigations two days later: Hb 6.9 mmol/L, Ht 0.32 L/L, MCV 102 fL, thrombocytes  $38 \times 10^9$ , leukocytes  $3.4 \times 10^9$ , eosinophils  $0.0 \times 10^9$ , basophils  $0.0 \times 10^9$ , granulocytes  $9 \times 10^9$ , lymphocytes  $2.1 \times 10^9$ , monocytes  $0.3 \times 10^9$ . Thus, an unexplained reduction in two of the three cell lines was seen, indication for a bone marrow puncture, performed by a pediatric oncologist. The aspirate revealed an aplastic bone marrow. Specific genetic investigations were performed as part of the workup of aplastic anemia, and Fanconi anemia mutations were discovered.

Since diagnosis patient A has regularly been seen at our outpatient clinic and sporadically at the emergency department, with persistent epistaxis and fever without origin (requiring empirical intravenous antibiotics). At the age of 11, patient A underwent an allogenic stem cell transplantation. Since her treatment, she has not had any somatic complaints and her blood count is persistently normal. Her 5-year-old brother underwent screening for FA.

Patient B, the 5-year-old brother of patient A was completely asymptomatic and without congenital deformities or anomalies. However, genetic screening also revealed FA in him. His blood count showed: Hb 6.7 (6.0-9.0) mmol/L, Ht 0.31 (0.30-0.42) L/L, MCV 90 (70-90) fL, thrombocytes  $143 (150-600) \times 10^9$ , leukocytes  $4.1 (4.0-15.0) \times 10^9$ , eosinophils  $0.0 (<0.8) \times 10^9$ , basophils  $0.0 (<0.2) \times 10^9$ , granulocytes  $1.6 (1.5-9.0) \times 10^9$ , lymphocytes  $2.1 (1.0-6.5) \times 10^9$ , monocytes  $0.3 (0.1-1.0) \times 10^9$ . He showed no clinically relevant signs of FA for 6 years. At the age of 11, he had decreasing cell lines and recurrent infections. He underwent an allogenic stem cell transplantation early 2019. He, too, has been without somatic complaints since the transplantation.

## 2.1 | Fanconi anemia

### 2.1.1 | Etiology

Fanconi anemia is caused by a mutation in one or more of thirteen different genes, Fanc A to N, all of which have an autosomal recessive inheritance except one, that is inherited via an X-chromosome. The gene complex plays an important role in correcting DNA replication errors.<sup>1,2</sup>

The disease is characterized by congenital anomalies in 60%-70% of patients.<sup>5</sup> The anomalies seen in patient A, with the exception of the scapula alata, are frequently seen with Fanconi anemia. Furthermore, skin deformities, such as café-au-lait spots, abnormalities of the thumb/radius, urinary system, and gastrointestinal tract have been described.<sup>5</sup> Due to the congenital anomalies, 4% of the patients are diagnosed during the first year of life. However, the diagnosis is mostly only made between the sixth and ninth year, commonly due to complaints related to anemia, thrombocytopenia, or leukopenia.<sup>1</sup> Symptoms include malaise, epistaxis, and recurring infections.

In addition to the anomalies, as a result of the failing DNA-repair system, malignancies are relatively common, especially head-neck, cervix, and breast tumors. Due to the reduced hematopoietic stem cells, there is an increased risk of bone marrow failure and the development of acute myeloid leukemia.<sup>5</sup>

### 2.1.2 | Treatment

Current treatment consists primarily of supportive care. Infections are treated with empirical antibiotics, and erythrocyte and thrombocyte transfusions are administered if needed. The only curative treatment is an allogenic stem cell transplantation. A large proportion of the patients will receive an indication for transplantation with disease progression. Until present, the results of stem cell transplantation in these patients have been disappointing, with a high risk of rejection and failure of the graft.

The poor bone marrow transplantation results are an important factor in the long-term poor prognosis in FA: 80% of the patients succumb before the age of 40.<sup>5</sup>

## 3 | DISCUSSION

In retrospect, the diagnosis of FA was initially missed in patient A, despite comprehensive evaluation of her congenital abnormalities.

The congenital malformations of FA affect multiple systems including the skeletal, ocular, auditory, renal, genital, and central nervous systems. The severity of these anomalies varies in patients. Because of the variety and the multiple

anomalies in our presented patient, genetic testing, specifically for FA following birth, is indicated, although genetic testing at the time was more limited than in current modern medicine. In retrospect, considering her medical history, laboratory investigations were indicated at first presentation at our outpatient clinic, prior to referral to the orthopedic surgeon and pediatric neurologist. The earlier the diagnosis of FA is made, the earlier appropriate therapy can be initiated.<sup>6</sup>

In Fanconi anemia patients, various skeletal abnormalities have regularly been described. However, scapula abnormalities are quite uncommonly reported. Only one other case of an abnormal scapula has been described in medical literature.<sup>4</sup> The authors described a scapula alata with scoliosis and hypoplasia of the scapula. A scapula alata is either an extremely rare abnormality in Fanconi anemia or an independent abnormality, in which case patient A has comorbidity. When skeletal abnormalities are found in young patients be aware of the possibility of FA, consider a complete blood count and look for anemia, thrombocytopenia, and neutropenia, and especially look for a high MCV even in the absence of cytopenias, in order to rule out Fanconi anemia. Patient A is only the second reported patient with FA and scapula alata, while scapula alata occurs more frequently. We would therefore not recommend a complete FA workup should only a scapula alata be present in a patient. However, a full blood count, as mentioned above, might be wise. In the presence of cytopenias or high MCV, patients should promptly be referred to a pediatric hematologist.

#### AUTHOR CONTRIBUTIONS

Renee van Adrichem, MD: was primary author of the manuscript. She also assisted in gathering relevant scientific background and references. Vincent de Weger, MD: assisted in writing the manuscript. He also assisted in gathering relevant scientific background and references. Daniel Broere, MD, pediatric neurologist: played a vital role in the diagnosis of patient A. He critically reviewed the manuscript. Femke van Herrewegen, MD, pediatric hemato-oncologist: is the treating physician of both patients. She assisted with describing the clinical problems and follow-up. She also critically reviewed

the manuscript. Jeremy Amaya, MD, orthopedic surgeon: assisted in the diagnosis of the scapula alata. He assisted in reviewing the diagnostic and therapeutic possibilities. He also critically reviewed the manuscript. Gavin William ten Tusscher, MD, PhD, pediatrician: was initially the treating physician of patient A. He supervised the writing and editing of the manuscript. He is the corresponding author.

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