

## Patient with Severe Hemophilia A Initially Diagnosed and Managed as Juvenile Idiopathic Arthritis

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### Abstract

**Background:** Hemophilia is an inherited bleeding disorder due to a deficiency in coagulation factor VIII (hemophilia A) or IX (hemophilia B). Bleeding can occur spontaneously, or after trauma, in muscles, joints, intracranially or within the gastrointestinal mucosa. Hemophilic arthropathy, which is due to repetitive bleeding into large joints, will occur in those with severe hemophilia if a prompt diagnosis is not made and treatment with factor replacement is not initiated.

**Case Presentation:** We report a case in which a 6-year old male presented with repetitive pain and swelling into his joints. He was initially diagnosed with juvenile rheumatoid arthritis and treated as such for 3 years. Extensive bleeding after dental extractions led to the diagnosis of severe hemophilia A. Scheduled factor VIII replacement was initiated, although due to recurrent bleeding episodes which occurred prior to his hemophilia diagnosis, joint damage was already present.

**Conclusions:** This case demonstrates the importance of considering hemophilia in the diagnostic work-up of a male patient with a swollen joint to prevent long-term joint disease and hemarthrosis.

**Keywords:** Hemophilia; Hemarthrosis; Pediatric; Juvenile Idiopathic Arthritis

### Abbreviations

aPTT: Activated Partial Thromboplastin Time; CBC: Complete Blood Count; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; HTC: Hemophilia Treatment Center; JIA: Juvenile Idiopathic Arthritis; NSAIDs: Nonsteroidal Anti-Inflammatories; DMARDs: Modifying Antirheumatic Drugs; PT: Prothrombin

### Introduction

Deficiencies of coagulation factor VIII or IX are known as hemophilia A and B respectively. This X-linked recessive disorder causes bleeding, particularly in the joints, due to factor VIII and IX having a major role in secondary hemostasis and the formation of the fibrin clot [1]. Hemophilia predominantly affects males due to an X-linked recessive inheritance pattern, with an equal prevalence in all races and ethnic groups. Some females are also clinically affected (known as symptomatic carriers) due to X-chromosome inactivation called lyonization. Hemophilia A occurs 1 in every 5,000 male births, and hemophilia B occurs 1 in every 20,000. Currently in the United States there are approximately 20,000 people living with either hemophilia A or B [2].

The timing and severity of the clinical presentation depends on the factor level; those with severe disease tend to present during infancy, and those with moderate and mild disease may not present until later in childhood. Patients can present with bleeding into muscles, as well as mucocutaneous bleeding, such as easy bruising, epistaxis, gastrointestinal bleeding and intracranial bleeding. However, the hallmark of hemophilia is bleeding into joints. While most joint bleeds occur in the knees, ankles and elbows, bleeding can occur in any joint. These hemarthrosis typically present with swelling, pain and warmth of the affected joint. Persons with severe hemophilia can have so-called spontaneous joint bleeds meaning essentially that there was no antecedent trauma.

Once suspected, the diagnosis of hemophilia is straightforward. The activated partial thromboplastin time (aPTT), a commonly available coagulation screening test, is essentially always abnormally prolonged. Such a result should lead to prompt testing for plasma factor VIII and IX activity levels, which will reveal the diagnosis. Of note, hemophilia is divided into three subtypes dependent on the patients' native factor level: mild (5 - 40%), moderate (1 - < 5%) or severe (< 1%).

The basis of treatment for hemophilia is also relatively straightforward, although there are numerous subtle nuances and thus a hematologist trained in managing patients with hemophilia should be consulted as soon as a diagnosis is made or even suspected. Intravenous factor replacement is used to treat bleeding episodes, either prophylactically to prevent bleeding, or as needed during an acute bleeding event. Standard of care management, in countries with access to factor, is to begin regular, prophylactic infusions of factor in persons with severe hemophilia after their first joint bleed [3]. Patients who are not appropriately diagnosed and treated will progress to debilitating arthropathy due to repetitive bleeding into the joint space causing damage to the cartilage and synovia [4].

Another cause of joint pain and swelling in children is juvenile idiopathic arthritis (JIA). JIA is chronic, autoimmune condition diagnosed in children less than 16 years of age where symptoms of joint inflammation persist for at least 6 weeks [5]. There are 7 categories of JIA: rheumatoid factor positive, systemic, oligoarthritis, polyarticular arthritis, psoriatic arthritis, enthesitis related arthritis and other arthritis [6]. The incidence of JIA in the U.S. ranges between 6.5 to 15 per 100,000 children, which is about 4,800 - 11,000 new cases of childhood arthritis diagnosed yearly [7]. By definition, JIA includes all types of arthritis with no apparent cause, lasting more than 6 weeks, in patients aged less than 16 years at onset. The diagnosis of JIA requires the exclusion of all other etiologies of arthritis in children, which can range from a vasculitis, an orthopedic condition, an infection or malignancy. Treatment for JIA is aimed at limiting the inflammatory flares with the goal of placing the patient in long-term remission by using the least toxic medication. The stepwise treatment approach typically begins with nonsteroidal anti-inflammatories (NSAIDs) and progress to glucocorticoids and then biologic and nonbiologic disease modifying antirheumatic drugs (DMARDs).

Patients with hemophilia and JIA can both present with joint pain and swelling, yet their treatments are vastly different. Misdiagnosis of either condition can lead to recurrent joint damage and long-term debilitating arthritis. We describe a case of a young male who presented with recurrent painful and swollen joints and was diagnosed and treated for JIA. After 3 years without improvement in symptoms and worsening arthropathy, he was appropriately diagnosed with severe hemophilia A. This case is particularly significant because the most common etiologies of a painful and swollen joint were ruled out in our patient except a bleeding disorder.

## Case Presentation

A 3-year old, previously healthy male initially presented to his pediatrician with left knee swelling and an inability to bear weight after a fall. He continued to limp for 2 weeks after this incident, but fully recovered with rest, ice and NSAIDs. Family history was significant for childhood arthritis in the mother and type 2 diabetes in the paternal grandfather; there was no history of other autoimmune or coagulation disorders. One year later, swelling and pain of his left knee recurred without a history of trauma. Shortly after, he had pain and decreased movement of his right elbow. He was without fever, rashes, weight loss, hair loss or oral ulcers. He had a normal complete blood count (CBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Radiographs of his knees were without signs of fracture or joint effusion.

His pediatrician referred him to rheumatology who found him to have chronic swelling of his right elbow with a 10 degree flexion contracture, without acute joint pain. He was given the diagnosis of anti-nuclear antibody (ANA) negative, HLA-B27 negative oligoarticular JIA. He was treated with twice daily naproxen for the pain and inflammation.

Eight months later he continued to have repeated episodes of right elbow, left knee, as well as left ankle pain and swelling (Figure 1). He also had bruises on his lower extremities. He continued without fever, rashes or abdominal pain. He was then started on weekly methotrexate and leucovorin, as well as naproxen. His ESR at that time was 10 mm/hr and he had a normal CBC. He received serial casting of his right elbow with a night splint for eight months. At 6 years of age, without improvement of his symptoms, his rheumatologist escalated therapy by adding etanercept to his current regimen of methotrexate and leucovorin.



**Figure 1a**



**Figure 1b**

**Figure 1:** Lateral and AP radiographs of patient's right elbow just prior to being diagnosed with hemophilia. Note the soft tissue swelling, joint effusion, advanced ossification, subchondral irregularity and cyst formation in the proximal ulna with abnormalities of the trochlear fossa.

Due to the increased immunosuppressive therapy, he underwent dental extractions to fix multiple cavities and tooth abscesses. The procedure went well without any complications, with only 40 ml blood loss. However, after the procedure he had intermittent oozing for 4

weeks. Due to the ongoing blood loss, he became weak and presented to our emergency department with hemoglobin of 5.7 g/dl, a normal white blood cell count and platelet count. His iron studies were consistent with iron deficiency anemia. His height was 117 centimeters (26<sup>th</sup> centile) and weight was 22 kilograms (48<sup>th</sup> centile) at this time. He was admitted and given a red blood cell transfusion.

Due to his prolonged post-surgical bleeding, he had coagulation studies performed which showed a normal prothrombin (PT) of 10.3 seconds (reference range 8.8 - 12.5 seconds), an aPTT of 40 seconds (reference range 23 - 29 seconds), with a normal 1:1 correction of 28 seconds. Factor VIII activity was significant for a level of < 1%, signifying severe hemophilia A, which was consistent with his history of repeated joint swelling in multiple joints which in retrospect were clearly joint bleeds.

He was started on recombinant factor VIII replacement three times a week at 40 units per kilogram through peripheral infusion to prevent any further bleeding. He was slowly weaned off of his rheumatologic medications and he was transferred to the hematology service. He continues on three times weekly recombinant factor VIII peripheral infusions at 30-40 units/kilogram and attends twice-weekly physical therapy due to right elbow and left ankle hemarthrosis and weakness. With regular prophylactic factor infusion, he has not had a joint bleed for over 2 years.

### Discussion

Hemophilia is a rare disease, but the diagnosis once considered is quite straightforward. Most patients with severe hemophilia will be diagnosed at birth through family history, however 30% of cases occur in the absence of a positive family history [8]. The first joint bleed most commonly occurs by the age of 4, but it can vary between 6 months and almost 6 years of age depending on the severity of hemophilia [9]. Patients with severe hemophilia typically present at a much younger age than those with mild or moderate hemophilia, when a bleed is more likely to be secondary to an injury or surgical intervention, rather than being spontaneous.

Our patient presented with knee swelling and pain at 3 years of age after a mild fall, which took 2 weeks for full recovery. This singular episode of a prolonged recovery after a simple fall should have raised concern of a more sinister underlying process. Unfortunately, he continued to have further episodes of recurrent knee pain and swelling in the same joint without injury, as well as pain in another large joint. Even without any systemic inflammatory signs or elevation of inflammatory markers, he was diagnosed with a rheumatologic disorder and an alternative diagnosis, such as a bleeding disorder, was not entertained. Furthermore, lack of improvement of his condition with anti-inflammatory and anti-arthritis medications combined with other signs of bleeding like bruising, should have led to the consideration for hemophilia as a possible diagnosis.

As such, we suggest that any male patient who presents to rheumatology with swelling of a large joint should be evaluated for hemophilia, even if the patient is lacking other signs of bleeding, like bruising or hematomas. Simple coagulation testing including a PT and aPTT should be performed. An abnormality in either should prompt consultation with a pediatric hematologist/oncologist who can guide further evaluation.

Since the treatment for hemophilia is so effective with many patients leading normal lives with an absence or near complete absence of bleeding, prompt diagnosis is of utmost importance. Delayed diagnosis can lead to permanent joint damage as occurred in the patient herein reported. Patients with hemophilia should also be referred and evaluated in a hemophilia treatment center (HTC), which offers multidisciplinary management focused on preventive care, the treatment of complications of the disease as well the psychosocial component of a chronic disease.

### Conclusion

This case demonstrates that hemophilia may mimic JIA given that both present with joint swelling and pain. As such, we strongly urge that any children (especially boys given the X-linked mode of inheritance) presenting with joint swelling should be evaluated for hemophilia. Although hemophilia may not be the most common cause of arthritis in children, its diagnosis can be made quickly and easily by

checking the aPTT. Making the proper (and early) diagnosis of hemophilia is crucial given that effective therapies are available and only prompt treatment can prevent permanent joint damage.

### Conflict of Interest

There are no financial interests or conflicts of interest with any of the authors.

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