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Case Report

Fibrodysplasia Ossificans Profressiva: The Importance of the Early Recognition and a Dramatic Case Report

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Abstract

Fibrodysplasia ossificans progressiva (FOP) is a rare, disabling genetic condition characterized by congenital malformations of the great toes and progressive heterotopic ossification (HO) in specific anatomic patterns. FOP is the most catastrophic disorder of HO in humans.

Fop is rare and affects 1:1, 4 million births [1].

FOP flare-ups are episodic; immobility is cumulative. A common mutation in activin receptor IA (ACVR1), a bone morphogenetic protein (BMP) type I receptor, exists in all sporadic and familial cases with a classic presentation of FOP. Approximately 97% of individuals with FOP have this recurrent mutation. Approximately 3% of affected individuals have a variant mutation in ACVR1, but all individuals with FOP have mutations in the ACVR1 gene.

Individuals with FOP appear normal at birth except for characteristic malformations of the great toes that are present in all classically affected individuals - 97% [2]. During the first decade of life, most children with FOP develop episodic, painful inflammatory soft tissue swellings (called flare-ups) [3]. These are often mistaken for tumors. Misdiagnosis is common and iatrogenic harm is high.

The FOP gene was identified in 2006 and until that year many people were already diagnosed with FOP just by the observation of its clinical features [4].

Since the recognition of the malformed big toes at birth can raise the possibility of the diagnostic of FOP at birth, the authors believe that this simple inspection of the toes at birth can decrease significantly the number of misdiagnosis and procedures that can do harm to the patient.

Keywords: Fibrodysplasia Ossificans Profressiva (FOP); Heterotopic ossification; Bone morphogenetic protein; Activin receptor I.

Case Report

M, female, Caucasian, was born and diagnosed with increased muscle tension. Since birth, she was under the care of a neurologist and a physiotherapist that prescribed and administered her physiotherapy and massages that according to the doctor would decrease the muscular tension of her body.

The patient's mother noticed that her big toes looked different from "*normal*" at birth. When she brought this to the attention of the doctors, she was informed that it was just a hallux deviation, which was a normal characteristic of the girl's body. She was told that there was no cause for concern.

When M was one month old the mother noticed that her head started to take a different shape and asked a neurologist and physiotherapist about it. Their opinion was that her sleeping position was the root cause and advised special pillows and physiotherapy.

After four months the patient was referred to a neurosurgeon who after a head scan, MRI and biopsy of a nodule on the scalp (Figure 1) said the patient had Desmoid Fibromatosis.

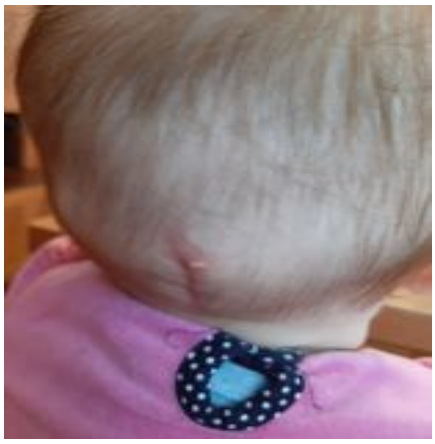

Figure 1: Place where the biopsy was performed.

An operation was performed to remove the bone with the tumor. The doctor transplanted the bone from the top of her head Figure 2.

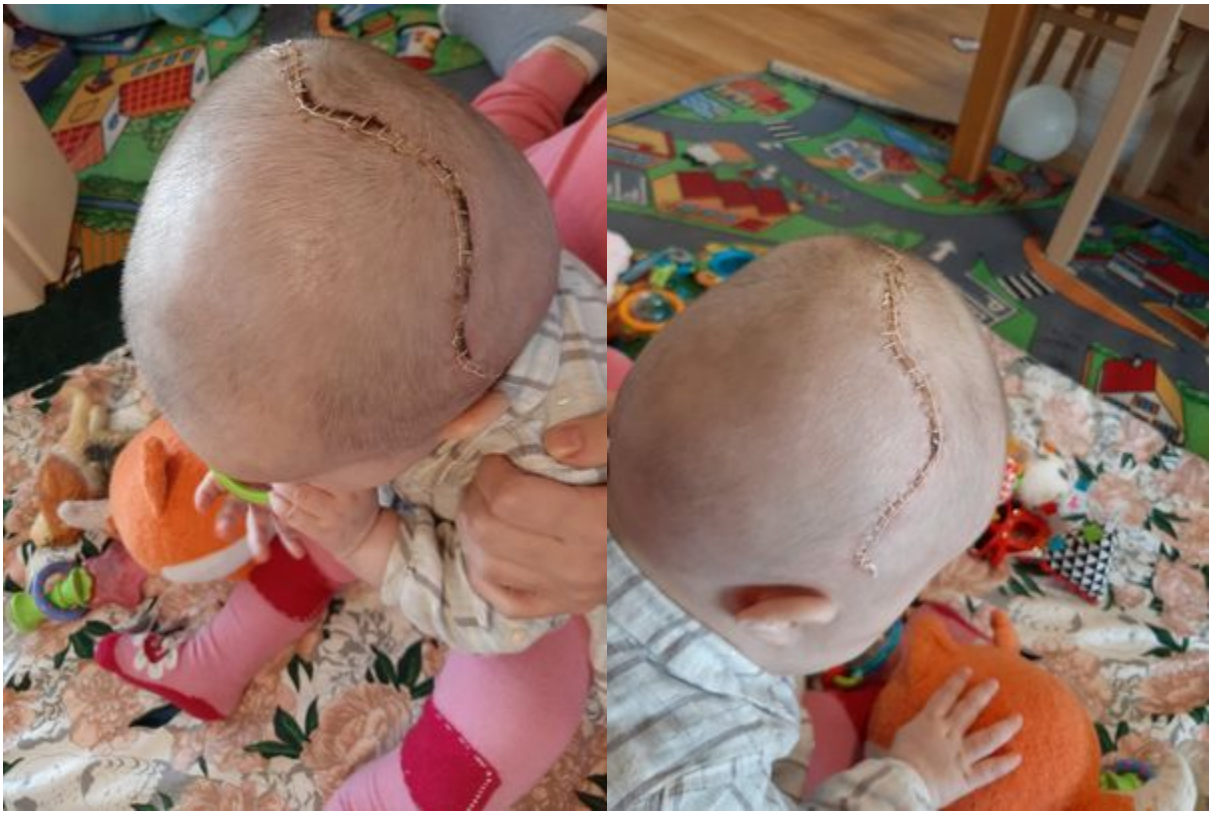

Figure 2: Transplanted the bone from the top of her head.

After the surgery the patient couldn't move her head and the neurologist said it was a result of the operation and she needed more physiotherapy. As a result, the patient had more pain and many new tumors started to appear on the neck and back. Chemotherapy was prescribed.

M had 17 cycles of chemo.

After some months she wasn't able to raise her hands, and had a big swelling on her neck and on the right side of her throat. Chemotherapy was interrupted and steroids were administered which seemed to help. During this episode the mother heard for the first time (from a doctor or a medicine student) that her daughter might have FOP. A blood sample for DNA tests was taken and the patient was sent home. Nothing else was said, no advice was given.

The diagnosis was confirmed, and the family was encouraged to find a specialist. They were told that nothing could be done to help their child; there was no cure, and she would be permanently disabled.

The patient's family started to search for answers on the internet.

The patient is now 1 year and 9 months old.

Discussion

Fibrodysplasia ossificans progressiva is a very rare genetic disease that affects 1 in each 1, 4 million people. It is a disease that highlights first principles of medical ethics and its golden rule for all health care professionals: **First, do no harm.**

The body of a person with FOP creates heterotopic bone (HO) inside muscles, tendons, and ligaments. These bones cross the joints and with time movement becomes impossible. These extra bones can't be removed because any trauma, whether a bump, an intramuscular injection (including vaccines or any kind of surgery, may lead to the catastrophic formation of more HO.

Malformed big toes are a telltale sign of FOP (97% of cases).

FOP can be recognized and confirmed based on clinical signs and symptoms.

The gene, that when mutated, causes FOP (ACVR1), was discovered on April 2006. For more than 30 years before this discovery diagnosis was clinical and confirmed by radiography, CT scan, or MRI.

The simple observation of the malformed big toes at birth indicates that the patient might have FOP (Figure 3). At this point all unnecessary procedures or immunizations must be avoided until more clinical signs or symptoms appear, or a genetic test can be performed.

Patients that have FOP may not have the malformed toes, and sometimes malformed toes are observed in patients who do not have HOP. However, screening for malformed toes is a simple, low-cost, and painless way to begin the diagnosis process.

In the case of M, had her malformed big toes been recognized by her medical team as a possible sign of FOP, and the relevant evaluation done at that time, M would have avoided extensive and unnecessary life altering medical intervention.

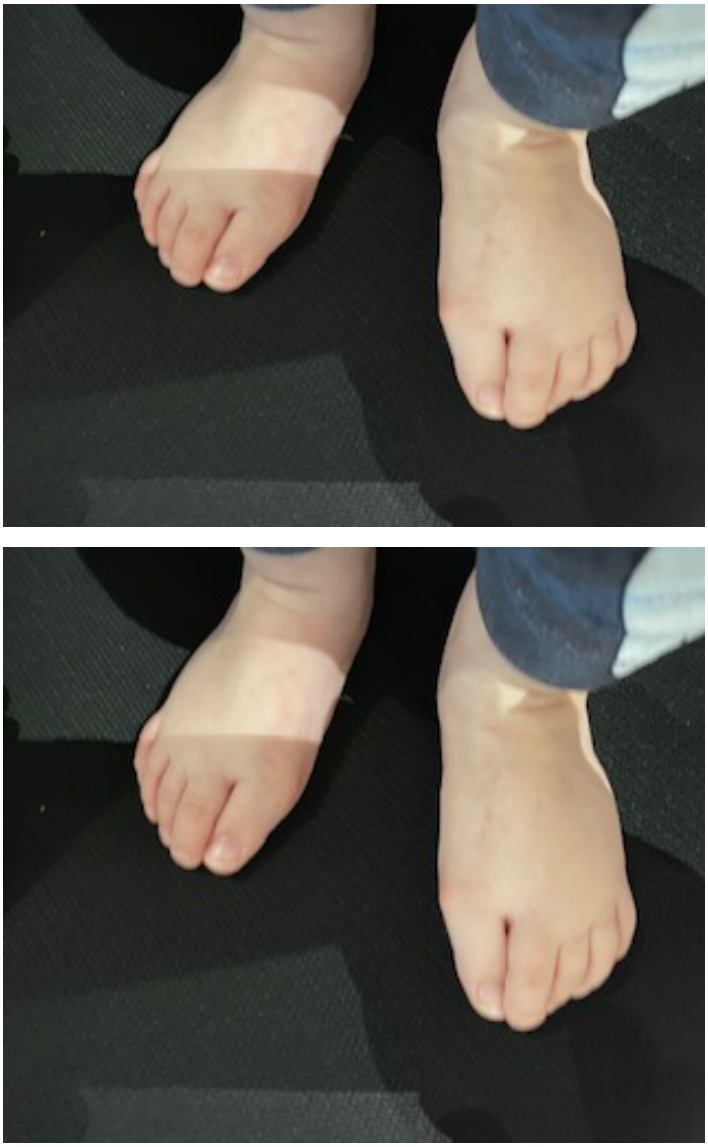

Figure 3: Big toes at birth indicates that the patient might have FOP.

There are some who propose that delaying diagnosis enables happier infancy. As demonstrated in the case report, later diagnosis, while it may be well intended, can have catastrophic consequences. In the words of M's mother: What I do know now is being empowered and to know as a young mother "*what-to-do*"

and "*what-not-to-do*" was a gift and a relief.

This case report is about surgery and chemotherapy, but childhood vaccinations are also often a trigger for FOP, and it is important to be aware that IM injection puts a person with FOP at risk.

Conclusion

The hope is that this case report will bring awareness of FOP to the medical profession, preventing and minimizing unnecessary and harmful tests and procedures. Once a diagnosis has been made, the parent and child can be directed to a care pathway that includes consultation with centers and specialists for rare diseases. Telling a patient there is nothing to be done is tantamount to medical negligence. Providing families with appropriate information and access to local organizations and support systems such as ICC, and IFOPA is an essential part of this care pathway.

This approach empowers families with the knowledge they need to make informed care decisions and maximize quality of life.

Evaluating newborns:

"*Newborn screening*" and genetic testing for certain diseases are important and lifesaving. The protocols for testing, informing families of their options, and related follow-up and support are equally important. There are additional conditions where malformed toes may be present at birth, not just FOP. This is important to keep in mind as any evaluating/testing protocols are further developed.

Proposed procedure:

- All newborns have their big toes examined at birth (no cost).
- A check box must be populated – malformed big toes ( ) yes ( ) no.
- If the answer is yes, all unnecessary procedures - surgeries, immunizations, intramuscular injections - must be suspended.
- If available, a genetic test to confirm the diagnosis is ordered. These should be provided by the government at no cost to the patient. If a genetic test is not available or affordable, the patient should be monitored for other clinical symptoms by a specialist.
- Patient is referred to a center with experience in FOP (ICC specialists around the world) and to a local and international association (IFOPA)
- Even with these protocols in place, we will miss some FOP patients who do not present with malformed big toes. We will also find patients with this presentation who do not have FOP. This should not, however, deter us from pursuing an approach that will help provide early diagnosis and care to the vast majority of FOP patients.

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