



## Case Report

# 2 Years Old Boy Diagnosed as the Extremely Rare Farber Disease in Qatar

Authors

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## Introduction

Farber lipogranulomatosis is ASAH1-related disorders that is inherited in an autosomal recessive manner meaning, each sibling of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Siblings with the same two pathogenic variants would be expected to have the same (or very similar) phenotype. The disorders are ultra-rare and estimated to occur in fewer than one per million.<sup>[1]</sup>

**Keyword:** Farber disease, genetics

## Case Presentation

We are reporting a two year old baby boy the third of his siblings (all healthy) who is born vaginally after full term pregnancy and around 3.9kg a product of consanguineous marriage (parents are cousins)

After birth specifically after the BCG vaccination the mother notice that he had a lump in the left axilla which at that time spontaneously disappeared

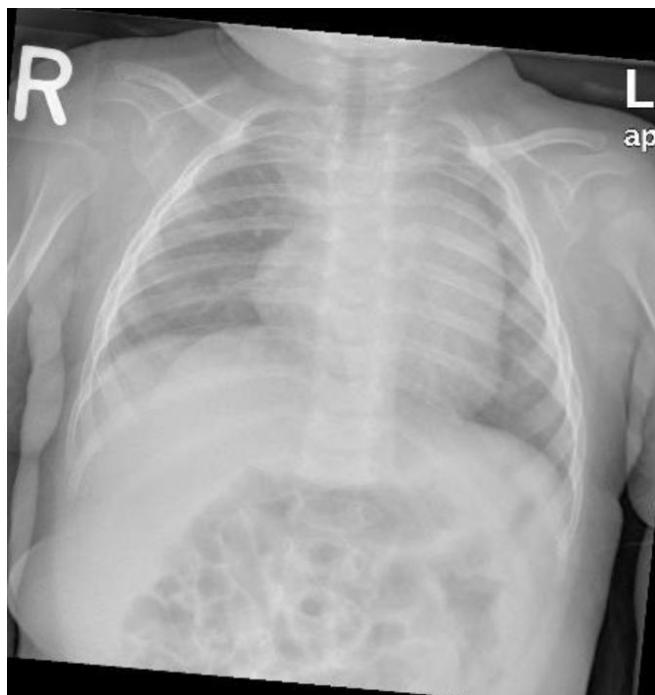
As part of having his regular vaccination follow ups it was noticed that the baby was having 4<sup>th</sup> bilateral toes anomaly with left auricle deformity, when parents first complained that thigh skin folds

inequal, he was referred back and forth to orthopedics with multiple pelvis ultrasound scans and x-rays all reports came with comments of slanted acetabulum mainly on left and rest of examination was unremarkable as shown in image (1)



**Image (1)** pelvic x-ray showings slanted acetabulum mainly left side

On date 12<sup>th</sup> January 2020 baby had an upper respiratory tract infection symptoms that necessitate a chest X-ray for his chest that revealed generalized osteopenia As shown in image (2)



**Image (2)** chest X-ray for his chest showing generalized osteopenia

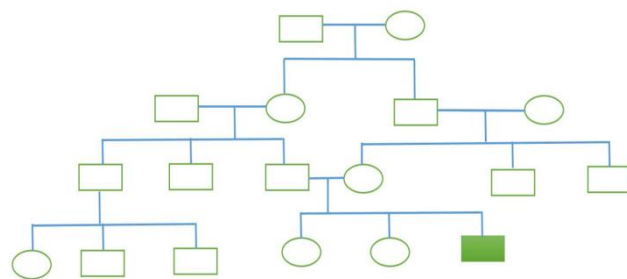
3<sup>rd</sup> February 2020 : at age of 7 months he was seen by his pediatrician and his mother mentioned that there was reappearance of the left axilla lump with an around 5x5 cm size that appeared to be mobile non tender with no signs/source of infection back then however other lymph nodes were not palpable she also complained of “weak crying quality “ with frequent secretions most of the time and recurrent common colds she highlighted the fact that the child since 4 month started to gradually become more stiff all over the body accompanied by weak hand grasp and fuzzier whenever changing diapers his assessment was noticeable for developmental delay which was as baby was not able to sit with support along with stiffness all over also he hardly turned from side to side when lying down with back preference, yet he was thriving / feeding well, vitally stable baby with an average growth parameters for height and weight although his head circumference was smaller than what it should be for his age normal Percentile he was toughly examined to confirm the weak cry ,anterior fontanelle of a fingertip , left lump "axilla " around 5x5 cm , the BCG scar is normal +dry along with stuffy nose, high arch palate

cardiopulmonary exam was unremarkable, abdomen soft and lax no organomegaly, normal back exam, normal male genitalia with small penis ,CNS exam confirmed stiffness of all limbs and weak grasp reflexes with hand extended and absent knee reflex there was equivocal planter reflex no clonus noticeno fasciculation with red reflex normal .

Initial laboratory workup: showed iron deficiency anemia and was treated accordingly

We referred him to pediatric (neurology / genetic/ ID /rheumatology) teams for further assessments

On his first genetic visit initial a pedigree of family was prepared as shown in diagram (1) below



Family pedigree (1) circle=female , square= male, shadow square= affected male

Also the team requested (Amino Acid Quantitative Plasma Ammonia Lactic Acid abdominal Ultrasound) that all came normal & Chromosomal Microarray Analysis DNA Banking reports :Genome wide array based comparative genomic hybridization (aCGH) with ~ 180,000 oligonucleotide probes yielded normal hybridization pattern for the genomic DNA obtained from this patient’s peripheral blood sample. The aCGH analysis did not identify any DNA copy number changes of known clinical significance in this male patient.

neurology team suggested further MRI scan of head which revealed: an isolated right cerebellar remote micro-hemorrhage. ID team workup diagnosed him with Tuberculosis (found by PPD screening prior to starting arthritis treatment)

Finally at the 14 months of age with further case deterioration wasn’t not able to roll or crawl

mostly because of painful joints, He was only bubbling with no words although (pediatric rehabilitation, neurology, rheumatology and infectious disease team were on board) clear symptoms and signs summary of : Global developmental delay/Microcephaly/Failure to thrive/ Stridor and dysphonia/ dysphagia/ Severe polyarticular arthritis with joint contractures/BCG lymphadenitis/Tuberculosis (found by PPD screening prior to starting arthritis treatment)/? immunodeficiency

which urged genetic team to have comprehensive genetic testing including whole exome sequencing (WES)the results showed that the patient is homozygous for a variant of uncertain significance in the ASAHI gene [p.Gly213Glu (GGA>GAA): c.638 G>A in exon 8]. The proband's mother, father and sibling are heterozygous for the the p.G213E variant in the ASAHI gene. The other sibling does not harbor the p.G213E variant in the ASAHI gene. Observed in homozygous state in this patient with ASAHI-related clinical features referred for genetic testing at GeneDx and not observed in homozygous state in controls.

Since the ASAHI pathogenic variants have been identified in this family, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible. given the diagnosis of Farber lipogranulomatosis and decision of management is symptomatic and multidisciplinary: For FD, may include gastrostomy tube placement, surgical removal of oral and airway granulomas, and treatment of seizures as per standard practice.

Hematopoietic stem cell transplantation: may be an option in affected individuals who do not have significant neurologic involvement. It improves the peripheral manifestations of Farber disease, but may not prevent the progressive neurological deterioration.

As surveillance patients at each visit would be assessed for growth with emphasis on feeding and nutritional status; airway, joint mobility, and developmental milestones.

## Discussion

Farber disease is one of the extremely rare, progressive, autosomal recessive lysosomal storage diseases happened due to deficiency of the acid ceramidase enzyme. Acid ceramidase that breaks down ceramide into sphingosine and fatty acid.<sup>[2]</sup>

If this enzyme is deficient, it will leads to the accumulation of fatty material (called ceramide) in the lysosomes of the cells, causing the signs and symptoms of this disorder.<sup>[3]</sup>

Usually its symptoms develop over time. However the onset of symptoms and how quickly they progress vary from person to person.<sup>[4]</sup>most commonly include:<sup>[1]</sup>Bumps under the skin located at pressure points and joints, also called subcutaneous nodules, lipogranulomas, or granulomas and Swollen, painful joints with progressive limitation of range of motion resulting in contracture in addition to Hoarse voice/cry among other symptoms observed in some individuals with Farber disease that may include:<sup>[4][2]</sup> lung infections, developmental delay, muscle weakness, seizures, Systemic inflammation, Failure to thrive, Bone disease like erosion of bone near joints, osteoporosis, peripheral osteolysis and others like hepatomegaly and corneal opacities.

Genetically this disease is caused by variants in the ASAHI gene A gene that codes for the acid ceramidase enzyme. patients with Farber disease have two copies of this gene that are not functioning properly leading to the enzyme deficiency and Over 73 different gene variants have been reported to cause the disease. No definitive genotype-phenotype correlations are known.<sup>[5]</sup>This disease is inherited in an autosomal recessive manner meaning that Affected individuals inherit one copy of the gene that is not functioning properly from each parent. Each parent is a called a carrier and has one copy of the gene that is functioning properly and one that is not. Siblings of individuals with Farber disease have a 25% chance to also have Farber disease, a 50% chance to be a carrier like the parents, and a

25% chance of being unaffected and not a carrier.<sup>[1]</sup>

The *ASAHI* gene is well known to cause a condition called spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME).<sup>[1]</sup>

Diagnosis usually starts with its symptoms as the onset is typically in early infancy nevertheless it might occur later in life. Children with classic form of Farber disease develop typical symptoms within the first few weeks to months of life.<sup>[1]</sup>

Attention must be payed as cases with moderate or attenuated forms may develop symptoms at any time in childhood. Sometimes it is difficult to diagnose Farber disease because the symptoms can be misdiagnosed as Juvenile Idiopathic Arthritis (JIA).<sup>[6][7]</sup>

Diagnosis is confirmed by molecular genetic testing of the *ASAHI* gene or by measuring acid ceramidase enzyme activity.<sup>[1]</sup> Unfortunately

There is no disease specific treatment for Farber disease. But medications like specifically tocilizumab (an interleukin-6 receptor inhibitor), has been shown to improve inflammation and pain in some patients.<sup>[8]</sup> Bone marrow transplant may improve granulomas and inflammation in patients with little or no lung or nervous system complications.<sup>[9]</sup> Supportive therapies such as, respiratory support, physical therapy and mobility aids might be required.

Studies in cells and mice have shown proof-of-concept for enzyme replacement therapy for Farber disease.<sup>[10]</sup>

**Conflict of Interest:** None

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