Novel manifestations of Farber disease mimicking neuronopathic Gaucher disease

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Accepted 10 May 2021

To cite: Mhatre S, Muranjan M, Karande S, *et al*. *BMJ Case Rep* 2021;**14**:e240742. doi:10.1136/bcr-2020-240742

SUMMARY

Diagnosis of rare disorders requires heightened clinical acumen. When such disorders present with atypical or novel features, it adds to the diagnostic challenge. A 9-month-old female infant who had received a diagnosis of neonatal hepatitis due to cytomegalovirus infection at 2 months of age presented to our institute with developmental delay, fever, vomiting, feeding difficulty, breathlessness and features of elevated intracranial pressure due to hydrocephalus. Key examination findings with cholestatic jaundice as an early manifestation led to suspicion of type 4 Farber disease. Observation of hydrocephalus, hypertension, bilateral pinguecula and Erlenmeyer flask deformity of the femur were unusual findings for Farber disease. The child had few features (pinguecula, Erlenmeyer flask deformity and hydrocephalus) overlapping with Gaucher disease. Alternatively, prosaposin deficiency (Farber disease type 7) was another differential diagnosis. Diagnosis of Farber disease was confirmed by detection of foamy macrophages on skin biopsy and two homozygous missense variants in *ASAH1* gene.

BACKGROUND

Farber disease (OMIM 228000) is a rare, progressive, multisystem disorder resulting from mutations in the *ASAH1* gene (HGNC:735).[1] These mutations lead to deficiency of the lysosomal enzyme, acid ceramidase (EC 3.5.1.23) which deacetylates ceramide to sphingosine and free fatty acid. About 200 cases have been reported in literature.[2] Farber disease has been categorised into seven subtypes on the basis of organ involvement (lungs, liver, spleen, nervous system, heart, lymph nodes) and severity.[3] Typical manifestations are a triad of weak or hoarse voice, subcutaneous nodules and joint deformity or arthritis.[1] However, early diagnosis of Farber disease can be challenging in absence of typical manifestations and wide variations in the phenotypic spectrum. The present case illustrates the diagnostic journey of an infant with an evolving natural history distinguished by atypical early presenting features, late onset of typical features and novel manifestations.

CASE PRESENTATION

A 9-month-old female infant of Asian-Indian descent was referred to our Institute with fever, poor feeding, vomiting and breathlessness since 15 days. There was progressive loss of milestones: cooing, partial head holding and hand regard achieved at 6 weeks, 8 weeks and 3 months, respectively; were lost at 8 weeks, 10 weeks and 5 months, respectively. Only social smile was present at 8 months of age. She was born of a third-degree consanguineous union and delivered at 35 weeks gestation by caesarean section for severe oligohydramnios. Birth weight was 1900 g. The child was admitted at another institute at 2 months of age for jaundice, dark yellow urine and hepatosplenomegaly (onset from day 15 of life). Investigations were as follows: serum total bilirubin 126 µmol/L, direct bilirubin 94 µmol/L, aspartate aminotransferase (AST) 8.62 ukat/L, alanine aminotransferase (ALT) 1.66 ukat/L, alkaline phosphatase 12.55 ukat/L, prothrombin time (PT) /partial thromboplastin time /International normalised ratio (INR) of 11.1/34.5/1, respectively, and serum alpha fetoprotein 87 107 µg/L (normal 19–21 878 µg/L for healthy premature infant aged 61–90 days).[4]

Abdominal ultrasonography had shown mildly enlarged liver with increased echotexture suggesting liver parenchymal disease. Liver biopsy was reported as neonatal hepatitis (disrupted liver parenchymal architecture, feathery degeneration and ballooning of hepatocytes, occasional giant cell transformation, intrahepatic and intracanalicular cholestasis and lymphocytic infiltration of portal tracts). The infant was discharged with provisional diagnosis of cytomegalovirus (CMV) hepatitis on the basis of positive serum CMV IgM titre (positive ratio 1.1) and IgG titre of 60 (positive >10 IU/AU/mL). Diagnostic testing by CMV antigenemia, CMV PCR or CMV culture was not performed. Jaundice resolved by 3 months of age with symptomatic treatment.

On inquiry after presentation to our institute, parents recollected noticing hoarse cry and decreased limb movements in their child since she was 2 months of age. At 5 months, they had observed erythematous and painful swelling involving knee and elbow joints. When the child was 6 months of age, the parents recollected that their child had developed complaints of intermittent vomiting, bulging anterior fontanelle and intermittent downward gaze of eyes. For these complaints, an MRI brain had been done at a local imaging facility at 8 months of age which showed decompensated communicating hydrocephalus (severe dilatation of lateral and third ventricles with periventricular hyperintensity on T2 weighted and fluid-attenuated inversion recovery images).

On admission at our institute, the infant was afebrile with pulse rate of 80/min, respiratory rate of 44/min and blood pressure of 146/96 mm Hg (>99th centile). Weight was 4.1 kg (Z score less than −3, WHO growth standard), length 64 cm (Z score between −2 and −3) and head circumference

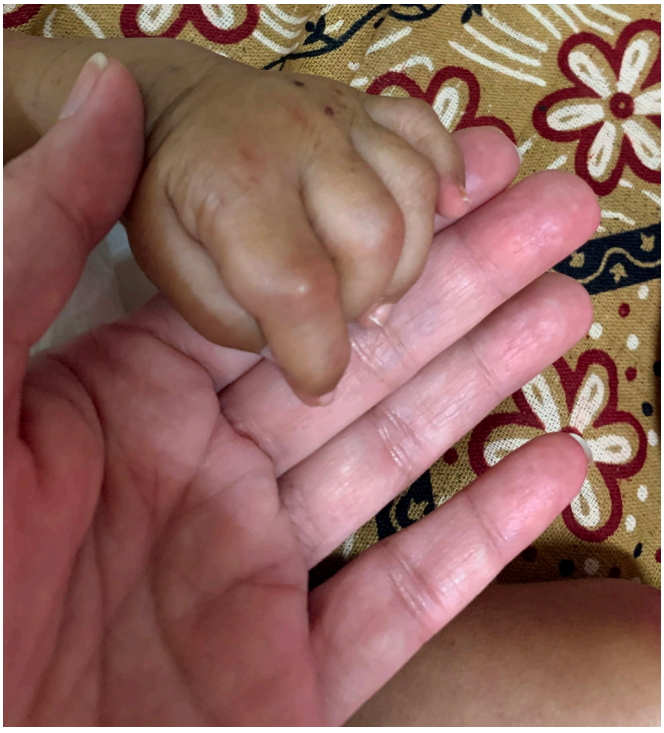

Figure 1 Clinical photograph showing joint contractures and subcutaneous nodules over the hand.

39.5 cm (Z score less than −3). There was pallor, pitting pedal oedema and bulging, non-pulsatile anterior fontanelle. Subcutaneous nodules (figure 1) were present bilaterally over proximal and distal interphalangeal, metacarpophalangeal, wrist, elbow and ankle joints. Additionally, there were multiple joint contractures involving knee, ankle, elbow, wrist and fingers. Ocular examination revealed bilateral medial pinguecula (figure 2). The child was fixing and following light intermittently, pupillary light response was sluggish, menace reflex was absent and there was bilateral papilledema. There was no chorioretinitis. Tone, power and deep tendon reflexes were diminished. There was hepatosplenomegaly (liver 6 cm and spleen 2 cm). Bilateral rhonchi were present all over the lung fields with reduced air entry. Cardiovascular system examination was normal.

INVESTIGATIONS

Salient blood investigations were as follows: serum total proteins 51 g/L, serum albumin 26 g/L, serum total bilirubin 17 µmol/L, direct bilirubin 8.5 µmol/L, AST 5.3 ukat/L, ALT 2.42 ukat/L, alkaline phosphatase 3.42 ukat/L and PT/INR of 13.4/1.04. Results of serological tests for hepatitis A, B, C and E viruses were negative. Cerebrospinal fluid (CSF) examination was normal. Chest radiograph, abdominal ultrasonography and renal

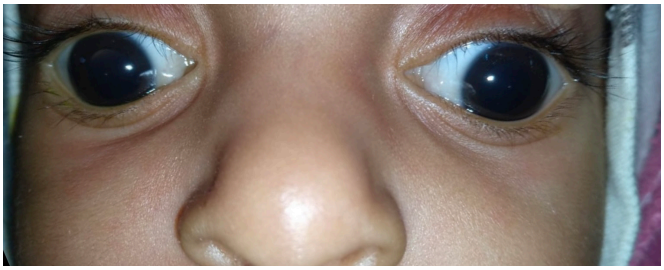

Figure 2 Pinguecula over the medial conjunctiva of both the eyes.

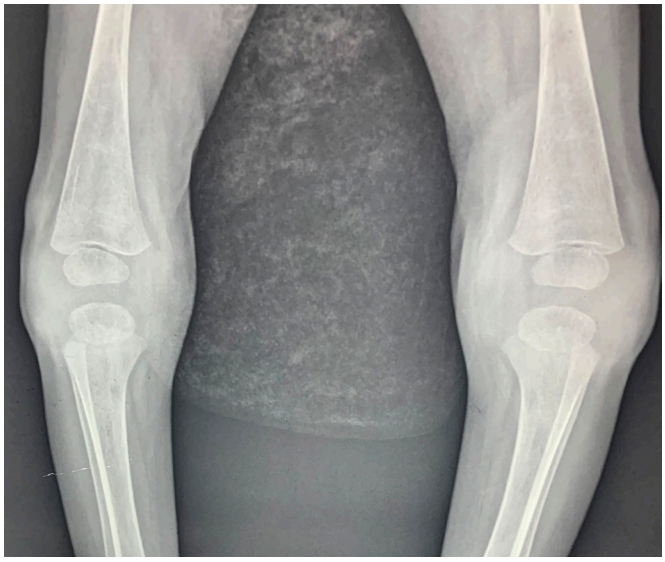

Figure 3 Lower limb radiograph showing generalised osteopenia and bilateral Erlenmeyer flask deformity of the lower end of femur.

doppler were normal. Skeletal survey revealed generalised osteopenia and Erlenmeyer flask deformity of distal femur (figure 3). CT scan of the brain showed severe dilatation of lateral and third ventricles with communicating hydrocephalus and absence of intracranial calcifications (figure 4). Targeted screening for aortic and cardiac valvular calcification by CT chest was normal. Leucocyte β glucocerebrosidase activity was normal (5.5 nmol/hour/mg protein, normal range 4–32). Plasma chitotriosidase activity was elevated: 2518 nmol/hour/mg protein (normal range 28.66–62.94). Review of original liver biopsy slides reported a possibility of lysosomal storage disease due to cells with foamy cytoplasm and some lipid content which appeared pale on

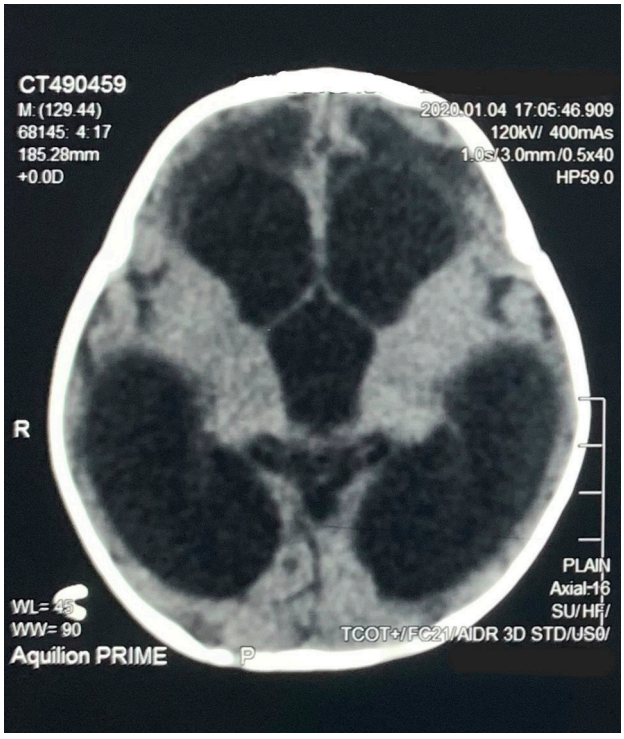

Figure 4 CT scan of the brain showing moderate to severe communicating hydrocephalus.

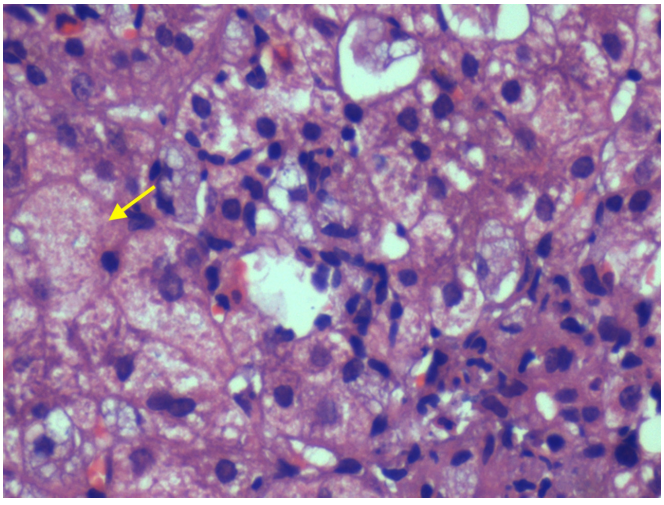

Figure 5 Liver histopatholgy (40× H&E) showing sinusoids with large macrophages having foamy cytoplasm with microvesicular changes (arrow). This appearance of lipid laden cells suggests a lysosomal storage disease.

Periodic acid-Schiff (PAS) staining (figure 5). Histopathological examination of subcutaneous nodule showed a diffuse dense nodular infiltrate of foamy histiocytes (figure 6A,B). Clinical exome detected two homozygous missense variants in exon 1 and exon 14 of ASAH1 gene, c.29A>T (p.Lys10Ile) and c.1233G>C (p.Trp411Cys), respectively. Our patient most likely had type 4 Farber disease.

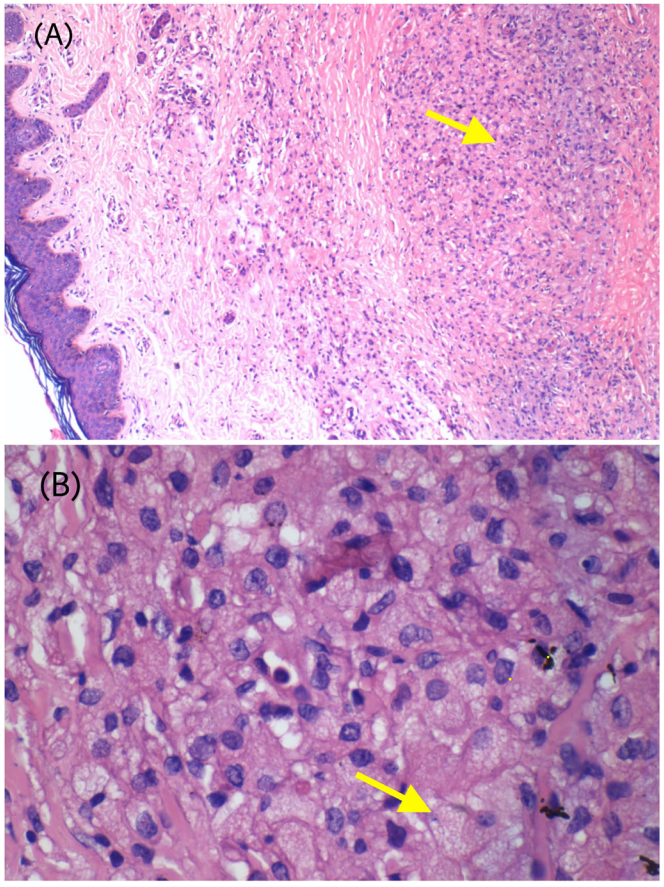

Figure 6 (A) Skin biopsy (10× H&E) showing diffuse dense nodular infiltrates of foamy histiocytes (arrow) involving the entire dermis. (B) Histiocytes (arrow) showing abundant pale foamy cytoplasm and a small centrally located nucleus (40× H&E).

DIFFERENTIAL DIAGNOSIS

This child was referred to our institute for surgical intervention with suspicion of hydrocephalus attributed to CMV infection in the past in view of positive CMV serology, neonatal hepatitis, prematurity and developmental delay. Congenital CMV infection is symptomatic in just 10% of cases and permanent sequelae develop in 40%–58% of symptomatic cases.[5] The proportion with permanent sequelae in those with asymptomatic congenital CMV infection is 13.5%.[5] Diagnosis of congenital CMV infection is made by virus culture combined with immunofluorescence or PCR from urine, saliva, blood or tissue specimen.[6] CMV IgM is not useful for diagnosis in infants beyond 2–3 weeks of age due to its low specificity and high cross reactivity.[5 6] In absence of diagnostic tests, positive serum CMV IgM titre at 2 months of age may not favour congenital infection but suggests perinatal infection. Perinatal CMV infections in immunocompetent host are asymptomatic with no long-term sequelae.[6] Hydrocephalus is known to develop in fetal CMV infection, but is extremely rare in postnatally acquired CMV infection.[7] Thus, an alternative aetiology for hydrocephalus was most likely in the present case.

We noted the typical triad of Farber disease on obtaining a meticulous history and physical examination: weak and hoarse voice, joint swelling, and subcutaneous nodules. History also confirmed presence of neuroregression rather than developmental delay. However, presence of communicating hydrocephalus, Erlenmeyer flask deformity of femur and pinguecula were unusual manifestations for Farber disease. Erlenmeyer flask deformity and osteopenia are common manifestations of Gaucher disease,[8] pinguecula is also described,[9] and hydrocephalus is a feature of a variant of neuronopathic Gaucher disease which may also be associated with cardiac valvular calcification. Thus along with hepatosplenomegaly and anaemia, our patient also had other unusual overlapping manifestations of Gaucher disease. The clinical dilemma was whether our patient had a rare coincidental occurrence of two diseases or a single disease, namely Farber disease with novel manifestations. Therefore, beta glucocerebrosidase enzyme activity was tested and normal activity ruled out Gaucher disease.

Another diagnostic possibility in our patient was prosaposin deficiency (type 7 Farber disease) caused by pathogenic variants in the *PSAP* gene. Prosaposin deficiency causes overlapping phenotypes due to multiple enzyme deficiencies: glucocerebrosidase (Gaucher disease), ceramidase (Farber disease) and galactocerebrosidase (Krabbe disease) as prosaposin is the precursor molecule for the four saposins required for activation of specific lysosomal hydrolases, including glucocerebrosidase and ceramidase.[1 10] Prosaposin deficiency was ruled out in our patient as no variants were detected in the *PSAP* gene by clinical exome sequencing.

TREATMENT

The child received supplemental oxygen at 10 L/min, intravenous cefotaxime (150 mg/kg/day in two divided doses for 5 days) and intravenous 20% mannitol 3 ml/kg three times a day. Ventriculoperitoneal shunt (VP shunt) was inserted for hydrocephalus on day 9 of admission. On day 11 of admission, the child developed septic shock requiring treatment with norepinephrine at 0.1 mcg/kg/min for 2 days and intravenous meropenem (40 mg/kg/dose three times a day) and vancomycin (20 mg/kg/dose four

times a day) for 16 days. Blood, urine and CSF cultures were sterile. Persistent hypertension required oral nifedipine (3 mg/kg/day), clonidine (20 mcg/kg/day) and enalapril (0.08 mg/kg/day). Child received two packed cell and three albumin transfusions for anaemia and hypoalbuminemia, respectively. On day 25 of hospital stay, child developed feed intolerance and ascites. Ascitic fluid examination suggested peritonitis. She also developed central line associated blood stream infection due to *Pseudomonas aeruginosa*. Hence VP shunt was exteriorised and intravenous colistin (25 000 U/kg/dose three times a day) and piperacillin–tazobactam (100 mg/kg/dose three times a day) were administered according to antibiotic sensitivity.

OUTCOME AND FOLLOW-UP

The child could be discharged after 39 days of hospitalisation on completion of antibiotic therapy. Parents received genetic counselling to explain disease prognosis, lack of definitive therapy for Farber disease, recurrence risk and future reproductive options. *ASAH1* gene sequencing was advised for parents to determine allele segregation. On telephonic follow-up subsequently, the child had died at 11 months of age. The parents have not yet got themselves tested due to financial constraints and the ongoing COVID-19 pandemic. We were therefore unable to obtain parental segregation of the two variants.

DISCUSSION

Farber disease is distinguished from other lysosomal storage disorders by the unique triad of weak or hoarse voice, subcutaneous nodules and joint deformity or arthritis.[1] However, there is a broad spectrum of manifestations and severity of disease. Thus Farber disease is classified in to seven subtypes: classical variant type 1, intermediate type 2, mild type 3, neonatal visceral variant type 4, neurological progressive variant type 5, combined Farber disease and Sandhoff disease type 6 and prosaposin deficiency type 7.[1] Our patient had unusual manifestations such as cholestatic jaundice and hypertension and manifestations overlapping with the phenotype of Gaucher disease such as hydrocephalus, pinguecula and Erlenmeyer flask deformity of the femora.[8] Of these, cholestatic jaundice and hydrocephalus are very rare manifestations of Farber disease.[1] Though xanthoma-like growths and inclusions in the conjunctival epithelial cells, stromal fibroblasts and endothelial cells have been described,[11] we did not find reports of pinguecula and Erlenmeyer flask deformity described in Farber disease among the largest series of 158 cases reported by Yu *et al* from 1952 to 2018.[1] Thus pinguecula and Erlenmeyer flask deformity are novel findings being reported in the present case of Farber disease. Erlenmeyer flask deformity results from abnormal bone modelling secondary to bone marrow infiltration in Gaucher disease.[12] Like Gaucher disease, bone marrow infiltration and chronic inflammation resulting from release of proinflammatory cytokines are also documented in Farber disease and could be the mechanism for development of Erlenmeyer flask deformity in Farber disease.[1 13] Pinguecula develops due to ellastotic degeneration of conjunctival stromal collagen.[14] Pinguecula has been reported in individuals with Gaucher disease and may sometimes demonstrate infiltration by Gaucher cells.[9]

Cholestatic jaundice is the presenting feature of type 4 Farber disease.[15] In the type 4 variant, the classical triad of clinical features is often absent early in the disease course as in the present case. Cholestatic jaundice in infancy as a manifestation of Farber disease is extremely rare. In one large series, 96 patients with Farber disease (median age of onset of 3 months, IQR from 1 to 9 months) were analysed for natural history, wherein cholestasis was not noted, though hepatosplenomegaly was noted in 25% of cases.[16] Thus when the classical triad is absent and cholestasis is the presenting feature, diagnostic delay is a rule rather than an exception. In the present case, cholestasis was mistakenly attributed to CMV hepatitis as elevated anti-CMV IgM antibody titre as the only evidence cannot be considered as conclusive proof of CMV hepatitis.[6]

Persistent hypertension requiring three antihypertensive drugs for control was an intriguing aspect in the present case. It could be speculated that hypertension may be secondary to nephropathy in Farber disease. Antonarakis *et al* described a female infant with Farber disease who had hypertension requiring four antihypertensive drugs for control.[17] Qualman *et al* later investigated her postmortem kidney specimens and documented nephropathy in Farber disease due to storage of granular material

Patient's perspective

Father's perspective: We had been referred to this institute for surgical repair of hydrocephalus in my child. We were therefore surprised to learn that the doctors were suspecting a rare genetic condition in my daughter. Numerous tests were performed to confirm diagnosis. The doctors arrived at the diagnosis of Farber disease and I was explained about the condition in depth and its management. Though we were disappointed to learn that there is still no cure for Farber disease, I wanted to put in all efforts towards my child's genetic testing and ongoing management. Nevertheless, I felt that the team of doctors attending to my child made the best possible efforts. Against odds, I was hoping for availability of curative treatment. I wish that in the near future, new definitive therapies are developed for such rare diseases. It was painful for my spouse and myself, to witness the effects of the disease progress, especially in the later stages when she was barely even moving a limb. Our only satisfaction was that in her last moments she was home and could be visited by close relatives. We urge the concerned authorities to provide services which make palliative care easier.

Learning points

- Manifestations of rare diseases like Farber disease (neonatal hepatitis and hydrocephalus in the present case) sometimes mimic clinical features of common paediatric disorders leading to diagnostic delay.
- Discriminating rare disease from common disorders requires a 'syndromic approach': meticulous history, careful physical examination and logical analysis of the symptom complex. Multisystem involvement or evolving clinical course would heighten suspicion of rare diseases, especially metabolic diseases like lysosomal storage disorders.
- Disorders like Farber disease have a variable spectrum of manifestations and severity. Awareness of the broad phenotypic spectrum is critical to recognise atypical presentations/symptoms.
- Phenotypic spectrum of rare diseases like Farber disease is often incompletely defined and overlapping manifestations with other disorders in the same biochemical pathway is possible. Thus, detecting novel findings requires comprehensive biochemical and molecular evaluation to establish correct aetiology.

in proximal tubular epithelial cells and PAS positive—diastase resistant storage material also stained by oil red O in glomerular capillary endothelium.[18]

The other unusual manifestation in our patient was hydrocephalus with signs of elevated intracranial pressure requiring VP shunt placement. Hydrocephalus has been detected in 70% of affected homozygous mice in mouse models of Farber disease.[19] All four ventricles are involved. Postulated mechanisms for development of hydrocephalus in Farber mice are excessive CSF production due to subcellular pathology in choroid plexus cells, reduced absorption of CSF due to granulomatous accumulation of microglia or macrophages in arachnoid granulations or secondary to brain atrophy.[19] Chedrawi *et al* have described a 2½ years old boy with Farber disease who had developed hydrocephalus accompanied by brain atrophy.[20] Presence of severe communicating hydrocephalus with raised intracranial pressure in the present case supports the speculated aetiologic role of increased CSF production, reduced CSF absorption and brain atrophy.[19]

The variants in exon 1 and exon 14 of the *ASAH* 1 gene identified in our child are novel. Of the two variants, the homozygous exon 1 variant could be the cause of disease in our patient. Exon 1 codes for the signal peptide and α subunit of ceramidase. The signal peptide is essential for lysosomal targeting of ceramidase.[13] Absence or structural alteration in the signal peptide would interfere with lysosomal targeting of the enzyme. The role of the second homozygous variant in exon 14 is presently uncertain.

Contributors MM, SM and SK were involved in clinical management of the patient. MM and SM reviewed literature and wrote the manuscript. SK critically reviewed the manuscript. HB performed and interpreted the skin biopsy. All authors have read and approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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