previously been reported in association with type II aldosterone synthase deficiency [8] in a consanguineous family of Middle Eastern European origin [8,9]. In addition, a compound heterozygous patient (T185I and a T498A substitution) has been also reported [6]. Interestingly, Macedonian nonconsanguinous immigrants in Australia were found to have the same genetic alteration [6]. A compound heterozygote showed a clinical phenotype of type II deficiency, with both detectable serum aldosterone and elevated 18-hydroxycorticosterone, but \textit{invitro} no residual aldosterone synthase activity [7].

In summary, the hormonal analysis classified the infant as ASD2. The penile hypoplasia can not, at this time be linked to any known cause. A coincidental occurrence cannot be excluded.

\textbf{Contributors:} All authors contributed to reporting and writing the manuscript.

\textbf{Competing interests:} None stated; \textbf{Funding:} None.

\section*{REFERENCES}

\section*{Novel Biochemical Abnormalities and Genotype in Farber Disease}

\textbf{MAMTA MURANJAN, SHRUTHI AGARWAL, KEYA LAHIRI AND *MURALI BASHYAM}

From the Genetic Clinic, Department of Pediatrics, Seth GS Medical College & KEM Hospital, Parel, Mumbai 400 012, and *Laboratory of Molecular Oncology, Centre for DNA Fingerprinting and Diagnostics, Hyderabad, Andhra Pradesh, India.

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\textbf{Correspondence to:} Dr Mamta Muranjan, Flat No. 301, Suman Apartments, 16 – B, Naushir Bharucha Road, Tardeo, Mumbai 400 007, India. muranjann@gmail.com

Received: April 27, 2011; Initial review: May 10, 2011; Accepted: June 27, 2011.
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\begin{abstract}
Farber disease caused by acid ceramidase deficiency is characterised by a triad of painful and swollen joints, subcutaneous nodules, and laryngeal involvement. A one year old female with overlapping features of the classical and type 5 variants is reported. Sialuria and elevated plasma chitotriosidase were unusual findings. A novel mutation of the \textit{ASAH1} gene was detected from DNA extracted from the umbilical stump.

\textbf{Key words:} \textit{ASAH1} gene, Acid ceramidase, Sialic acid, Chitotriosidase, Lysosomal storage disorders.
\end{abstract}

Farber disease (FD) (OMIM 228000) is a rare autosomal recessive disorder caused by acid ceramidase deficiency. This enzyme catalyzes the terminal step in glycosphingolipid metabolism, where ceramide is degraded to sphingosine and fatty acid. Less than 100 cases have been reported worldwide [1]. Present case had several unique biochemical findings and a novel mutation, and confirmation of diagnosis was done after death from preserved umbilical cord DNA.
CASE REPORT

A female infant born of an inbred consanguineous union presented at one year of age with developmental delay and loss of developmental skills. The antenatal period and labor was uncomplicated. Birth weight was 2.75 kg. Poor feeding and weak cry were noted in the first week of life. Social smile was attained at 3 months, by 4 months, she was grasping and visually tracking objects and turning her head towards sounds. At 6 months, the child was lethargic and feeding poorly with no neck control. At 8 months, the social smile was lost and at 9 months, there was loss of roll over, stranger anxiety, visual tracking, and response to sound. There was no history of seizures, involuntary movements, abnormal limb posturing, hyperacusis, abnormal increasing in head size or abdominal distention. Due to hypotonia and joint stiffness at 9 months of age, electromyogram at another hospital had shown a myopathic pattern. Nerve conduction, thyroid hormone levels and creatinine phosphokinase were normal. MRI revealed severe generalized cerebral atrophy, dilatation of the supratentorial ventricular system, widened basal cisterns and atrophic corpus callosum. BERA showed right sided severe sensorineural hearing loss and left sided mild hearing loss. On examination at one year of age, the weight, height and head circumference were all below the 5th percentile. Flexion contractures of the elbow, hip, knee, metacarpophalangeal and interphalangeal joints were present. There were multiple, firm, subcutaneous nodules measuring 0.5 to 1 cm in diameter over the knee joints and metacarpophalangeal and interphalangeal joints of the feet. The voice was weak and hoarse. Bilateral cherry red spot were detected. The child was irritable, not responding to commands and vocalization was absent. There was generalized hypertonia, power was 3/5, deep tendon reflexes were hypoactive, plantar response was flexor, menace reflex was absent and there was no response to sound. Coarse facies, hepatosplenomegaly and hernias were absent. Farber disease was suspected but the family declined to pursue investigations due to financial constraints and there was no follow-up.

Eight months later, the child was admitted with a febrile respiratory illness and succumbed to aspiration pneumonia. Radiographs did not reveal dysostosis multiplex. Leukocyte lysosomal enzyme activities for GM₁ and GM₂ gangliosidosidosis and Niemann-Pick disease were normal and normal activity of hexosaminidase and arylsulfatase A in plasma ruled out I-cell disease. Acid ceramidase activity could not be measured due to lack of facility. The plasma chitotriosidase was raised (427.48 mmol/hr/ml, normal of 45.8 ± 17.14). Urinary total and free sialic acid were elevated (4.4 and 2.8, normal of 1.01 ± 0.46 and 0.55 ± 0.24 mmol/gm creatinine, respectively).

As the family did not consent for an autopsy, the nodules could not be examined by histopathology. Fortunately, the umbilical cord had been preserved. DNA was extracted from the umbilical cord for ASAH_1 gene sequencing. The proband was homozygous for a novel IVS6 + 4 A > G mutation. Two polymorphisms were also detected: IVS1 - 3 C > T and IVS1 - 50 G > A. The parents were heterozygous for all the three changes. A heterozygote fetus was diagnosed by prenatal diagnosis in a subsequent pregnancy.

DISCUSSION

The spectrum of manifestations in FD range from the most severe presenting as hydrops fetalis, neonatal onset (type 4), early infantile onset variant (classic or type 1), and progressive neurologic form (type 1) to the milder phenotypes (type 2 and 3) [1]. Four cases of FD have been reported from India in the past 20 years [2, 3]. Seventeen ASAH_1 mutations have been reported to date worldwide [4]. Of these, 12 were missense mutations, two were intronic splice site mutations leading to exon skipping, and one each was a small insertion and deletion. This includes one other mutation reported in an Indian patient apart from the present [3]. All these are private mutations. It is a custom in many regions of the world including India to preserve the umbilical cord [5,6]. DNA has been extracted from umbilical cords preserved for up to 44 years for forensic investigations [5].

Our patient had overlapping features of type 1 (joint manifestations, evidence of myopathy and absence of significant hepatosplenomegaly and seizures) and type 5 (progressive neurologic disease and milder joint abnormalities and subcutaneous nodules) [1]. Normal hexosaminidase activity ruled out the type 6 variant. Unusual findings in our patient were the presence of sialuria and elevated plasma chitotriosidase. Sphingolipid is sequentially degraded within lysosomes to GM₃ ganglioside. Enzymatic degradation of GM₃ ganglioside (a sialoglycoconjugate) by sialidase leads to formation of lactosylceramide and releases sialic acid. Lactosylceramide is metabolized through an intermediate step to ceramide. [7] Thus elevation of total and free sialic acid in our patient was secondary to accumulation of precursor (GM₃ ganglioside) as a result of a downstream block in the metabolic pathway. Sialuria has also been reported before [8], along with accumulation of sulfatide and GM₄ ganglioside [9].

Elevation of plasma chitotriosidase has not been reported earlier in FD. Chitotriosidase is a chitinase expressed by activated macrophages [10,11]. More than 1000 fold elevations are observed in Gaucher disease. Chitotriosidase activity is also increased in several other...
lysosomal diseases as well as in diseases like glycogen storage disease type IV, Alagille disease, arteriosclerosis, β-thalassemia major, sarcoidosis and malaria [10,11]. Our case adds to the spectrum of lysosomal storage disorders with increased chitotriosidase activity. However, it is also possible that the nearly 10 fold elevation in our patient could be secondary to intercurrent infection as the enzyme level is high in bacterial and fungal infections due to inflammatory cytokines that augment production [11].

In conclusion, though manifestations of FD are unique, diagnosis can be delayed if symptoms are misinterpreted. Without the availability of acid ceramidase activity testing in India, tissue biopsy is diagnostic. However, availability of genotyping in India may replace the need for invasive histopathological diagnosis. DNA banking is an urgent necessity in circumstances where mortality in genetic disease like FD is early and unpredictable. This report serves to raise awareness amongst physicians for the need to preserve DNA in cases of suspected fatal genetic diseases.

Acknowledgments: The authors thank Dr Sanjay Oak, Director of Medical Education & Health for granting permission to publish this paper and Dr Chitra Prasad, Associate Professor of Genetics, Metabolism and Pediatrics, London, Ontario for her inputs.

Contributors: SA drafted the paper and performed literature search, MM diagnosed and investigated the case and revised the paper, KL provided intellectual inputs, MB performed the molecular analysis.

Funding: None; Competing interests: None stated.

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Pediatric Scrub Typhus in South Sikkim

NAVEEN GUPTA, VEENA MITTAL, *B GURUNG, *U SHERPA
From the Zoonosis Division, National Centre for Disease Control, 22, Sham Nath Marg, Delhi-110054; and *District hospital Namchi, South Sikkim, India.

We present five cases of paediatric Scrub typhus from Community Health Centre, Namchi, South Sikkim emphasize timely diagnosis of scrub typhus for appropriate management. Response to doxycycline was good, with fever subsiding within 48-72 hrs of starting the treatment. Four out of five cases completely recovered once appropriate medication was given.

Key words: Child, India, Scrub typhus, Sikkim.

Scrub typhus is endemic in regions of eastern Asia and the South Western Pacific (Korea to Australia) and from Japan to India and Pakistan [1-6]. Scrub typhus is prevalent in many parts of India but specific data are not available [7]. There have been outbreaks in areas located in the Sub-Himalayan belt, from Jammu to Nagaland. There were reports of Scrub typhus outbreaks in Himachal Pradesh, Sikkim and...