doses for cost considerations was not prudent since the child has developed a vasculopathy with renal scarring. Anti-TNF agents prevent and eliminate vasculitis symptoms in DADA2 patients with a remarkable reduction in ischemic stroke risk [6]. They decrease inflammatory burden of the disease, increase growth and development, and improve some hematological manifestations such as anemia and thrombocytopenia. Thalidomide has been reported useful in a large study. Aspirin and anticoagulants are contraindicated since hemorrhage may complicate the stroke. Hematopoietic stem cell transplantation can be curative in patients who present with bone marrow failure or are non-responsive to anti-TNF therapy [4].

In conclusion, pediatricians in India must be aware of this recently discovered entity and its myriad presentations, including PAN, early-onset strokes, arterial obliterations, immunodeficiency, and aplastic anemia. With high rates of consanguinity and endogamy in several parts of India, we believe more patients of hereditary auto-inflammatory diseases would be diagnosed with increasing physician awareness and availability of genetic testing.

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RAJU KHUBCHANDANI[1]* AND IVONA AKSENTIJEVICH[2]
[1]*Department of Pediatric Rheumatology, SRCC Children's Hospital, Mumbai, India; and*
[2]*Inflammatory Disease Section, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA.*
**rajukhubchandani@yahoo.co.in*

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Crisponi/Cold Induced Sweating Syndrome Type 1 With a Private Cytokine Receptor Like Factor 1 (CRLF1) Mutation in an Indian Family

Crisponi/cold induced sweating syndrome type 1 (CS/CISS1; Mendelian Inheritance in Man [MIM] #272430), a rare autosomal recessive disorder, is possibly under-recognised due to its complex phenotype with likely misinterpretation of symptoms. Worldwide, there are fewer than 100 reported cases and we present the second Indian patient with a *CRLF1* genetic mutation [1-4]. A 1½-month-boy presented with intermittent high-grade fever, episodic contractions of facial and neck muscles and feeding difficulties since birth. He was sixth born to a non-consanguineous healthy couple hailing from North India. There was history of two sibling deaths, a male and a female in third week of life. Both the babies were born at term gestation, had normal birth weight but associated with birth asphyxia followed by progressive feeding abnormalities and abnormal posturing. His three elder female siblings were all alive and healthy. There was history of one spontaneous abortion in mother. Antenatal course of the present pregnancy was uneventful; mother received 2 doses of tetanus toxoid. The baby was delivered vaginally at term gestation with a birth weight of 3.25 kg. He was non-vigorous with meconium stained liquor but cried after stimulation. He required NICU stay with oxygen therapy and intravenous antibiotics though all laboratory investigations including sepsis work up were within normal limits. At presentation at 1½ months of life, he had fever (103°F), tachycardia, tachypnea, SpO2 of 98% at room air but clear chest. He was underweight (3.7 Kg) with normal length (60 cm) and head circumference (36.5cm). He had a round expressionless face (***Fig.*****1a**) with bilateral camptodactyly and clinodactyly with adduction of thumbs (***Fig.*****1b**) and overriding of the toes of both feet (***Fig.*****1c**). Neurological examination revealed a weak cry and decreased spontaneous motor activity. There were paroxysms of facial and neck muscle contraction leading to puckering of lips, tight eye closure, neck extension (***Fig.*** **1d**) along with inward rotation of the upper limbs and clenching of the hands lasting a few minutes. These episodes were associated with crying and often precipitated by tactile or painful stimulation with a frequency of 25-30 episodes during daytime. Episodes were absent during rest and sleep. Partial remission was obtained with clonazepam administration. Initially, possibilities of hypoxic ischemic encephalopathy, neonatal sepsis with meningitis, neonatal tetanus, Sandifer syndrome and inborn error of metabolism were considered.

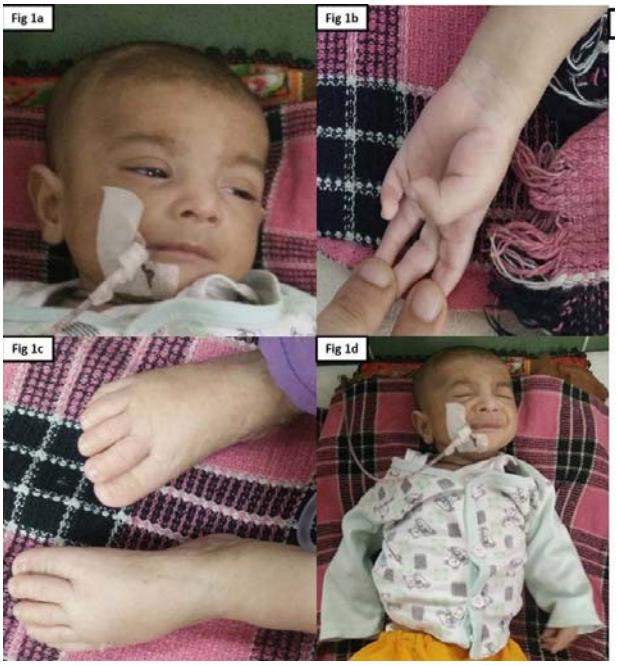

Fig.1 *A 1½-month-boy with 1a- round expressionless face; 1b- bilateral camptodactyly and clinodactyly with adduction of thumbs; 1c–overriding of the toes of both feet and 1d- paroxysms of facial and neck muscle contraction leading to puckering of lips, tight eye closure, neck extension.*

Laboratory investigations showed normal sepsis screen and sterile blood and urine cultures. Urine microscopy, cerebrospinal fluid examination, fundus, electroencephalography, chest *X*-ray, magnetic resonance imaging of brain, skeletal survey and ultrasound abdomen were normal. Metabolic screen (blood sugar, serum ammonia, arterial lactate, blood gas and urine ketones) was negative. ENT evaluation and *X*-ray temporo-mandibular joint (TMJ) ruled out TMJ ankylosis. 24-hour pH monitoring revealed mild gastro-esophageal reflux. Further literature search lead to a possibility of Crisponi/cold-induced sweating syndrome type 1 (CS/CISS1) and genetic analysis for its confirmation was done at the Institute of biomedical and genetic research, National research council, Italy. Molecular analysis carried out for all the nine *Cytokine receptor like factor 1* (CRLF1) [NM_004750.4] coding regions (including the exon-intron junctions) by sequencing analysis of the PCR products showed the presence of a homozygous small deletion [c.120delA;p. (Ala41Leufs*2)] in exon 2. This variant has very strong evidence of pathogenicity according to American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) 2015 guidelines classification (PVS1, PM2, PP4) and multiple algorithms predictions such as SIFT (damaging) and mutation taster (disease causing) [4]. Both parents as well as the two sisters were heterozygous, while the youngest sister was homozygous for the wild type allele, confirming the familial origin of the pathogenic variant. Genetic counselling was done for the family. The child was continued on orogastric (OG) feeds, anti-pyretics, lanzoprazole and clonazepam. He could gradually be weaned of OG feeds by 8 months of life but was subsequently lost to follow up.

CS/CISS1 is characterized by neonatal onset marked facial muscular contractions with trismus and abundant salivation, simulating a tetanic spasm precipitated by tactile stimulation or crying. There is associated intermittent hyperthermia, feeding problems (due to orofacial muscle spasms, poorly developed swallowing reflex, and associated gastroesophageal reflux (GER) and respiratory difficulties. A round face, broad nose with anteverted nostrils, small mouth, micrognathia and bilateral camptodactyly are typical [5]. It is usually lethal in the first few months of life. In rare surviving individuals, hyperthermia and muscle contractions may disappear after infancy while kyphoscoliosis and paradoxical cold induced sweating may develop towards the end of first decade; few may develop a mild psychomotor retardation [5,6]. Important differential diagnoses include neonatal tetanus (differentiated by absence of typical dysmor-phology), Stuve-Wiedemann syndrome (differentiated by lower limb bowing) and Freeman–Sheldon syndrome. CS/CISS1 is caused by variants in the *CRLF1* gene. Thirty-seven disease causing *CRLF1* pathogenic variants in 96 patients have been reported in the medical literature [1,4]. Although genotype/phenotype correlation has been elusive, it has been suggested that the level of the mutant protein may correlate with the phenotypic severity [4]. Treatment of CS/CISS1 is primarily symptomatic. Clonazepam for muscle spasms and moxonidine for cold induced sweating have been tried with variable response. Monitoring is recommended for development of kyphoscoliosis and psychomotor retardation [4,6]. The need for suspicion of CS/CISS1 in cases where the other common differential diagnosis have been ruled out and specially in presence of a suggestive family history is exemplified in the index case. Further, the role of genetic diagnosis for genetic counselling and preventing recurrence of the disease in the family cannot be over emphasized.

PUNEET KAUR SAHI,[1]* ANIRBAN MANDAL,[2] IVANA PERSICO,[3] ANJU SETH[4] AND LAURA CRISPONI[5]

Departments of Pediatrics, [1]Maulana Azad Medical College and Lok Nayak Hospital, New Delhi, India; [2]Sitaram Bhartia Institute of Science and Research, New Delhi, India; [4]Lady Hardinge Medical College and affiliated Kalawati Saran Children Hospital, New Delhi, India; [3]Istituto di Ricerca Genetica e Biomedica, Consiglio Nazionale delle Ricerche, Sassari, Italy; and [5]Istituto di Ricerca Genetica e Biomedica, Consiglio Nazionale delle Ricerche, Monserrato (CA), Italy.
*puneetksahi@gmail.com

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X-linked Lymphoproliferative Disease (XLP1) Presenting as Non-Epstein Barr Virus (EBV) - Related Hemophagocytic Lymphohistiocytosis (HLH)

X-linked lymphoproliferative disease (XLP1) is a rare immunodeficiency disorder with immune dysregulation, caused by *SH2D1A/SAP* gene mutations. Clinical manifestations include fulminant infectious mononucleosis (FIM), hemophagocytic lymphohistiocytosis (HLH), lymphomas and dysgammaglobulinemia [1]. HLH in children can be primary/familial HLH or secondary/reactive HLH [2]. In 80% of familial HLH cases the genetic defect can be identified. To the best of our knowledge this is the first report of XLP1 in an infant with non-Epstein Barr virus (EBV) HLH in India.

An 11 months old male infant, born to third degree consanguineous parents presented with intermittent fever and loose stools for twenty days. There was no history of vomiting, blood in stools, bleeding manifestations, cough/cold, weight loss or past recurrent infections with an unremarkable family history. Child had normal nutritional status, some pallor and massive hepatosplenomegaly. Investigations revealed anemia with hemoglobin of 8.3 g/dL, neutrophilic leucocytosis, absolute neutrophil count of 1704/mm3, low normal platelet count and along with elevated liver enzymes (alanine transaminase: 210 U/dL; aspartate transaminase: 399 U/dL). He was started on antibiotics ceftriaxone and doxycycline. Further investigations including smear for malarial parasite, serology for scrub typhus, cytomegalovirus, EBV and retrovirus was negative. As his fever spikes persisted, ultrasound abdomen, echocardiogram and Immunoglobulin profile were done and found normal. .

Re-evaluation revealed decreasing neutrophil counts (ANC of 624/mm^3), thrombocytopenia (platelet count of 0.49×10^9/L) and coagulopathy (INR of 1.6). Antibiotics were escalated to meropenem and vancomycin because of worsening clinical condition and laboratory parameters though the blood cultures remained sterile. In view of pancytopenia, deranged liver functions, organomegaly and persisting fever spikes, hemophagocytic lymphohistiocytosis (HLH) was considered. Follow up investigations showed elevated serum ferritin (5498 ng/mL), serum triglycerides (278 mg/dL), soluble CD 25 levels, decreased serum fibrinogen (175 mg/dL), bone marrow hemophagocytosis, and cerebrospinal fluid lymphocytic pleocytosis, all consistent with the diagnosis of HLH [2]. He was treated with intravenous immunoglobulin, dexamethasone and etoposide. Workup for primary HLH showed normal perforin protein expression and CD 107a. With the background of consanguinity and male sex, XLP was considered. Next generation sequencing revealed mutation in *SH2D1* characteristic of XLP1. Unfortunately, the child had HLH progression and expired of fulminant hepatic dysfunction and coagulopathy. Parents were counseled regarding antenatal diagnosis of XLP in next pregnancy.

X-linked lymphoproliferative syndrome (XLP) is a rare inherited immunodeficiency affecting approximately one in 1,000,000 males. XLP patients have severe immune dysregulation often after viral infection (typically with Epstein-Barr virus [EBV]) [1]. However, a proportion of boys (approximately 10%) have immunological abnormalities before evidence of EBV infection [3] like in our case.

One of the manifestations of XLP1 is hemophagocytic lymphohistiocytosis (HLH) which is a multisystem inflammatory disorder characterized by cytokine overproduction by activated lymphocytes and macrophages.

XLP arises from 2 different genetic defects in *SH2D1A,* in Xq25 gene (XLP1, the most common) and *BIRC/XIAP* gene (XLP2). *SH2D1A* encodes the cytoplasmic protein *SAP* (*SLAM*-associated protein) which is a key regulator of normal immune function in T cells and naturalkiller cells [4]. Defects in SAP lead to the varied immune defects in XLP1 patients. Our child had a mutation in *SH2D1A* confirming XLP1.

Hematopoietic stem cell transplantation (HSCT) remains the most effective curative treatment for XLP though IVIG and rituximab have been used previously in prevention with questionable benefit [4,5].

Any male child with HLH or FIM should undergo genetic testing for therapeutic implications like bone marrow transplant. Early genetic confirmation of diagnosis also plays a major role in prenatal diagnosis and genetic counselling for the next pregnancy.

AJEITHA LOGANATHAN,[1]* DEENADAYALAN MUNIRATHNAM[1] AND BALASUBRAMANIAN SUNDARAM[2]
Department of [1]Pediatric Hematology and Oncology and [2]Pediatrics, Kanchi Kamakoti CHILDS Trust Hospital,