Spectrum of Systemic Auto-Inflammatory Diseases in India: A Multi-Centric Experience

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Background: Systemic autoinflammatory diseases (SAID) are rare inherited disorders involving genes regulating innate immune signaling and are characterized by periodic or chronic multi-systemic inflammation.

Objective: To describe spectrum of clinical, immunological, molecular features, and outcomes of patients with SAID in India.

Methods: Request to share data was sent to multiple centers in India that are involved in care and management of patients with Inborn Errors of Immunity. Six centers provided requisite data that were compiled and analyzed.

Results: Data on 107 patients with SAID were collated—of these, 29 patients were excluded due to unavailability of complete information. Twelve patients (15%) had type 1 interferonopathies, 21 (26%) had diseases affecting inflammasomes, 30 patients (41%) had non-inflammasome related conditions and 1 five patients (19%) had Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA). Type 1 interferonopathies identified in the cohort included patients with Deficiency of Adenosine Deaminase 2 (DADA2) (six patients; five families); STING-associated vasculopathy infantile-onset (SAVI) (three patients, one family); Spondyloenchondro-dysplasia with Immune Dysregulation (SPENCD) (two patients). Diseases affecting inflammasomes include Mevalonate Kinase Deficiency (eight patients); Cryopyrin-Associated Periodic Syndromes (CAPS) (seven patients); NLR Family, Pyrin domain-containing 12 (NLRP12) (two patients); Familial Mediterranean fever (FMF) (two patients); Autoinflammation and PLCG2-associated antibody deficiency and immune dysregulation (APLAID) (two patients). TNF receptor-associated periodic syndrome (TRAPS) (three patients); A20 haploinsufficiency (four patients); Deficiency of Interleukin 1 Receptor Antagonist (DIRA) (two patients) were categorized as non-inflammasome related conditions. There were significant delays in...
INTRODUCTION

Systemic autoinflammatory diseases (SAID) are complex inherited disorders caused by defects in several genes regulating innate immune signaling and are characterized by periodic or chronic multisystem sterile inflammation (1–3).

The term “autoinflammatory disorders” was coined in 1999 by Daniel Kastner’s group when they proposed a new group of immunological diseases (4). The paper described genetic background of familial Hibernian fever, and rechristened it as “TNF receptor-associated periodic syndrome (TRAPS).” It also linked it with previously described mutations in Pyrin (MEFV) gene that causes familial Mediterranean fever (FMF) (4–6). In 2010, Kastner et al. defined autoinflammatory diseases as “clinical disorders marked by abnormally increased inflammation, mediated predominantly by cells and molecules of the innate immune system with a significant host predisposition” (1, 7). Eurofever registry and Pediatric Rheumatology International Trials Organization (PRINTO) have also proposed classification criteria for different hereditary recurrent fever syndromes (8).

SAIDs can be monogenic and polygenetic or multifactorial (9, 10). Monogenic SAID (e.g., TRAPS, FMF) follow Mendelian inheritance and result from pathogenic variants in a single gene. On the other hand, disorders such as systemic juvenile idiopathic arthritis, Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) syndrome and Adult-Onset Still Disease have polygenic or multifactorial etiology. The 2019 International Union of Immunological Societies (IUIS) Expert Committee classified monogenic SAID into 3 major groups: Type 1 interferonopathies, defects affecting the inflammasome and non-inflammasome-related conditions (11).

Over the last 2 decades due to an increasing awareness and availability of high throughput genetic sequencing techniques, there has been an exponential increase in discovery of genes responsible for SAID (2, 12, 13). Further, molecular insights of these disorders have provided the basis for new therapeutic interventions leading to improved outcomes and long-term survivals. There is paucity of data on SAID from India with published literature comprising of only anecdotal case reports (14–21). In this manuscript we describe clinical features, molecular profile, treatment and outcome in patients with monogenic SAID from six centers in our country. This paper reports nationwide cohort on SAID.

DEFINITION OF SAID

Several definitions have been proposed for SAID (4, 8, 11, 22). For the purpose of this study we have used European Society for Immunodeficiencies (ESID) working group definition for the categorization of SAID. ESID has defined “unclassified autoinflammatory diseases” to be characterized by recurrent fever (temperature >38°C) having occurred on at least six occasions with exclusion of other known infective/inflammatory autoimmune disorders and documented evidence of increased inflammatory markers [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)], age of onset under 40 years and predominantly but not exclusively with systemic symptoms (23). In the present study all patients who fulfilled ESID working group definition and had molecular confirmation of monogenic SAID were included. Patients with polygenic SAID (e.g., systemic diagnosis Corticosteroids and other immunosuppressive agents were used for treatment as anti-IL-1 drugs and other biological agents were and still are not available in India. Eight (16.3%) patients had so far succumbed to their illness.

Conclusions: This is the first nationwide cohort of patients with SAID from India. Clinical manifestations were diverse. Overlapping of clinical features with other relatively common rheumatological disorders often resulted in delays in diagnosis. More nationwide efforts are needed to enhance awareness of SAID among health care professionals and there is an urgent need to make targeted immunotherapies universally available.

Keywords: systemic autoinflammatory diseases, India, deficiency of adenosine deaminase 2, NOMID/CINCA, hyper IgD syndrome, A20 (TNFAIP3), inflammasome, Type I interferonopathies
juvenile idiopathic arthritis, chronic non-infectious osteitis) and infantile inflammatory bowel disease were excluded.

All patients were further classified into three subtypes according to 2019 IUIS classification for SAID (11). Coatamer complex one protein alpha subunit (COPA) syndrome was classified as Type 1 interferonopathy (24, 25). Patients without molecular confirmation of diagnosis and/or could not be classified in accordance with IUIS classification were also excluded. Some patients included in this series have been reported earlier and these have been duly cited (14, 17, 19, 26, 27).

### MOLECULAR INVESTIGATIONS

Molecular analysis of patients for PGIMER, Chandigarh was performed at Pediatric Allergy Immunology Laboratory at PGIMER, Chandigarh or in collaboration with international centers, namely Center for Autoinflammatory Diseases and Immunodeficiency, Genoa, Italy (1three patients) and National Institutes of Health (NIH), USA (three patients). Measurement of plasma adenosine deaminase 2 (ADA2) activity in extracts of dried plasma spots was performed in the laboratory of Dr. Michael Hershfield at Duke University School of Medicine, Durham NC, USA (28).

### LABORATORY INVESTIGATION AT PGIMER, CHANDIGARH

Molecular analysis of Nucleotide binding oligomerization domain 2 (NOD 2) gene in patients suspected to have Blau syndrome (11/14 patients) and Adenosine deaminase 2 (ADA2) deficiency was performed in-house in Pediatric Immunology Laboratory, Advanced Pediatric Center by Sanger sequencing. Exon-4 of NOD2 gene was amplified using specified oligonucleotide primers and results were analyzed using Codon Code Aligner software (Codon Code Corporation, Massachusetts, USA). Screening of hotspot region (exon 2) of ADA2 gene was also performed in patients clinically suspected to have Deficiency of Adenosine Deaminase 2 (DADA2).

Molecular analysis in most patients at other centers was carried out at commercial laboratories that use targeted gene panel by Next Generation Sequencing (NGS) techniques. Sanger sequencing was used to confirm the variants obtained by NGS.

### RESULTS

Data on 107 patients with SAID were collated from various centers in India. Of these, 19 patients had to be excluded as molecular confirmation was not available. Ten patients with variants of unknown significance (VUS) in genes associated with SAIDs were also excluded if found inconsistent with clinical profiles or non-pathogenic based on predictive analysis tools. Remaining 78 patients (Figure 1) included Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) (15 patients (19%) from PGIMER); type 1 interferonopathies (1two patients, 15%); diseases affecting inflammasomes (21 patients, 26%); and non-inflammasome related conditions (30 patients, 38%). Clinical details of patients with PFAPA (1five patients) and Blau syndrome (14 patients) are not being presented in the current manuscript (Suri et al., manuscript in submission).

### CLINICAL PROFILE OF PATIENTS WITH TYPE 1 INTERFERONOPATHIES

Type 1 interferonopathies identified in the cohort included patients with DADA2 (six patients; five families); STING-associated vasculopathy infantile-onset (SAVI) (three patients from one family); Spondylo enchondro dysplasia with Immune Dysregulation (SPENCD) (two patients) and Coatamer complex one protein alpha subunit (COPA syndrome) (one patient) (Table 1).

### DADA2

Age of onset of symptoms in patients with DADA2 ranged from 5 months to 17 years while age at diagnosis ranged from 9 months to 48 years. All patients with DADA 2 were diagnosed and managed as polyarthritis nodosa (PAN). Family history was contributory in three patients (patient no. 2, 3, and 5). Predominant clinical features included fever (4/5), recurrent stroke (3/5), vasculitic rash (3/5), and retinal changes (2/5). Patient one had presented with hypertensive stroke at 3.3 years of aging 1992 and had second episode at the age of 16 years in 2002. The diagnosis of DADA2 was established in 2018 after three decades of follow-up.

Patient no 3 was diagnosed to have central retinal artery occlusion. Inflammatory markers were persistently normal. His sister (patient two) was under treatment and follow up for PAN. She had presented with recurrent abdominal pain with perforation peritonitis and catheter angiography had revealed microaneurysms in mesenteric arteries and renal arteries (Figure 2). In view of family historyDAD2 was suspected and mutation in ADA2 gene was detected. Establishment of diagnosis lead to stoppage of aspirin and commencement of anti-TNF agents.

### SAVI

A 10-year-old girl (patient no. 7), previously reported (19) had presented with fever, polyarthritis, and interstitial lung disease (ILD). Initial diagnosis of juvenile idiopathic arthritis with ILD was considered. Younger sibling (patient no. eight) and father (patient no. nine) of index patient also had similar symptoms. Father gave history of gangrene of both lower limbs with amputation of right midfoot and left 2nd toe. Exome sequencing revealed pathogenic variant in Transmembrane protein 173 (TMEM173) gene confirming the diagnosis of SAVI.

### SPENCD

A 13-year-old girl (patient no 10) had persistent pyrexia, decreased vision with bilateral optic atrophy, hypertensive stroke, seizures, and proteinuria. Investigations showed hypergammaglobulinemia and positive antinuclear antibodies (ANA) with elevated anti-double stranded DNA (dsDNA) but normal complements. Initial diagnosis of systemic lupus...
erythematous was proffered. Renal biopsy revealed IgA nephropathy. Magnetic Resonance Imaging (MRI) brain showed basal ganglia calcifications. Exome sequencing revealed pathogenic variant in Acid phosphatase 5 (ACP 5) gene which was confirmed on Sanger sequencing.

A 4-year-old girl (patient no 11) had presented with bleeding manifestations (skin, mucosal and intracranial bleed) since infancy (Figure 3). She had steroid refractory anemia and thrombocytopenia with no autoantibodies and hypocellular bone marrow. She was later noted to have short stature and metaphyseal dysplasia along with bilateral basal ganglia calcification. Targeted gene panel revealed homozygous nucleotide deletion in exon 1 of ACP5 gene.

COPA Syndrome
The index patient (patient no 12), previously reported (30) was diagnosed to have COPA syndrome when they had presented with rheumatoid factor positive deforming polyarthritis and interstitial lung disease. His father also had arthritis and had succumbed to progressive lung disease.

CLINICAL PROFILE OF PATIENTS WITH DEFECTS AFFECTING THE INFLAMMASOMES

Twenty-one patients were classified to have inflammasomopathies (n = 21, 26%). These included Mevalonate Kinase Deficiency (HyperIgD syndrome) (eight patients); Cryopyrin-Associated Periodic Syndromes (CAPS) (seven patients); NLR Family, Pyrin domain-containing 12 (NLRP12) (two patients); FMF (two patients); Autoinflammation and PLCG2-associated antibody deficiency and immune dysregulation (APLAID) (two patients) (Table 2).

Hyper IgD Syndrome
Patients with Hyper Ig D syndrome (Patient no. 13–20) had onset of symptoms during infancy (15 days–1 year) with predominant clinical features being fever (7/8), rash (4/8), lymphadenopathy (4/8), hepatosplenomegaly (5/8), and anemia (4/8). Initial diagnosis of neonatal sepsis was considered in two patients (patient no. 13–14). Three patients were found to have the V377I Dutch founder variant and 2 had c.1129G>A variant which is fairly common in South India particularly Kerala (15).
TABLE 1 | Clinical manifestations, molecular profile, treatment, and outcome of patients with type I interferonopathies (n = 12).

| Center | Patient | Age of onset of symptoms | Clinical features | Laboratory features | Family history (Consanguinity/siblings affected) | Initial Diagnosis | Molecular details | Treatment details | Follow-up duration and outcomes |
|--------|---------|--------------------------|------------------|---------------------|-------------------------------------------------|------------------|-----------------|-----------------|----------------------|
| PGIMER | Pt. 1   | (31 y/M)                 | 3.3y             | Fever, Rash, Hypertension, Recurrent strokes at 3 and 16 years of age | CRP: 32 mg/L ESR: 20 mm/h MRI brain: multiple infarcts right MCA territory and right posterior circulation CTA: microaneurysms in branches renal artery Muscle biopsy: healed arteritis | Third degree consanguinity | PAN | ADA2 exon 2; c.140G>T; p.Gly47Val Homozygous missense Previously reported: Yes | CS, AZR, enalapril, aspirin Change in treatment after diagnosis: Aspirin stopped, HCQs added and planned for anti-TNF | 34 years and doing well |
|        | Pt. 2   | (13 y/F)                 | 5 y              | Fever, Recurrent abdominal pain, Hypertension, Optic atrophy, Left hemiparesis and facial palsy, Intestinal perforation | CRP: 45 mg/L ESR: 40 mm/h DSA: multiple microaneurysms involving bilateral interlobar and segmental branches of renal artery, branches of gastroduodenal artery, distal branches of SMA and IMA GI Biopsy: Ulcer, ischemic, gangrene, perforation in ileum. Chronic inflammation in recto-sigmoid junction Plasma ADA2 activity: 1.1 mU/g protein mL Plasma ADA2 activity (Father): 42.5 mU/g protein mL Plasma ADA2 activity (Mother): 69.5 mU/g protein mL | Sister of Pt. 3 | PAN | ADA2 exon 2; c.139G>C; p.Gly47Arg Homozygous missense Previously reported: Yes | CS, CYC (10 pulses), AZR, aspirin Change in treatment after diagnosis: Aspirin stopped, HCQs added and planned for anti-TNF | 8 year and doing well |
|        | Pt. 3   | (18 y/M)                 | 17 y             | Sudden Painless loss of vision, Raynaud phenomenon, CRAO | CRP: 10 mg/L ESR: 12 mm/h CTA: Normal study Plasma ADA2 activity: 0.3 mU/g protein mL | Brother of Pt. 2 | PAN | ADA2 exon 2; c.139G>C; p.Gly47Arg Same as the sibling (Pt. 2) | CS, CYC (6 pulses), AZR, aspirin, LMWH Change in treatment after diagnosis: Aspirin stopped, HCQs added and planned for anti-TNF | 3 years and doing well |
|        | Pt. 4   | (17 y/M)                 | (29)             | Fever, Vasculitic ulcers, Seizures, Recurrent stroke with neurological deficits, VFp Cranial Nerve palsy, median nerve neuropathy, GI bleed | Skin Biopsy: Necrotizing cutaneous vasculitis | No | PAN | ADA2 exon 2; c.139G>C; p.Gly47Arg; exon 2: c.278T>C; p.Ile93Thr Previously reported: Yes Homozygous missense variation | CS, AZR Change in treatment: anti-TNF commenced | 1 year and doing well |

(Continued)
| Center | Patient (Age at diagnosis/ Sex) | Age of onset of symptoms | Clinical features | Laboratory features | Family history (Consanguinity/siblings affected) | Initial Diagnosis | Molecular details | Treatment details | Follow-up duration and outcomes |
|--------|--------------------------------|--------------------------|------------------|---------------------|-----------------------------------------------|------------------|-----------------|-----------------|-----------------------------|
|        | Pt. 5 (48 y/M) (29) | 8 y | Fever<br>Ulcers and rash<br>Recurrent stroke along with neurological deficits, mononeuritis multiplex, CRAO | CRP: 5.11 mg/L<br>ESR: 30 mm/h<br>C3/C4: 129/32.3 | PAN | ADA2 exon 2; c.139G>C; p.Gly47Arg<br>Homozygous missense variation | Previously reported: Yes | CS, MMF<br>Change in treatment: Stopped aspirin | Doing well |
|        | Pt. 6 (0.9 y/F) (29) | 5 months | Fever<br>Anemia<br>generalized lymphadenopathy, splenomegaly | CRP: 102 mg/L<br>ESR: 155 mm/h<br>Bone marrow: Normocellular bone marrow with trilineage hematopoiesis<br>lgG: 1,640 mg/dL<br>lgA: 101 mg/dL<br>lgM: 96 mg/dL<br>lgE: 3.7 mg/dL | No | ADA2 exon 2; c.139G>C; p.Gly47Arg<br>Homozygous missense variation | Previously reported: Yes | Injection etanercept | Doing well |
|        | Pt. 7 (10 y/F) (19) | 0.91 y | Fever<br>Failure to thrive, Deforming inflammatory arthritis with contractures of small and large joints<br>ILD, corneal<br>Opacities in right eye | CRP: 97.23 mg/L<br>ESR: 120 mm/h<br>CT chest:ILD<br>RA factor: positive<br>ANA: 4+ RIM<br>lgG: >2.535 (540–1,610)<br>lgA: <436 (70–250)<br>C3: 166 mg/dl (89–187)<br>C4: 20 mg/dl (16–38)<br>Anti ds-DNA: 10.8 IU/ml (<25- Negative)<br>Serum IL-6: 3,700 pg/ml<br>Serum IL-10: 13,900 pg/ml<br>Interferon levels elevated | JIA, COPA<br>Brother and Father affected (Pt. 8 and Pt. 9) | TMEM173 exon5; c.463G>A; p.Val155Met<br>Homozygous missense variation | Previously reported: Yes | CS, MTX, AZR, Naproxen, HCQ | Alive |
|        | Pt. 8 (3 y/M) (19) | 2 y | Fever<br>Polyarthitis (bilateral knee, small joints of the hands)<br>Rash<br>ILD | CRP: 12.98 mg/L<br>ESR: 108 mm/h<br>CT chest:ILD<br>RA factor: negative<br>ANA: 2+ Speckled<br>IL-6: 3,500 pg/ml<br>IL-10: 14123 pg/ml<br>Interferon levels elevated | B/o Pt. 7 | TMEM173 exon5; c.463G>A; p.Val155Met<br>Homozygous missense variation | Same as Pt. 7 | AZR, MTX | Well |

STING-associated vasculopathy with onset in infancy (SAVI) (n = 3)

PGIMER

| Patient (Age at diagnosis/ Sex) | Age of onset of symptoms | Clinical features | Laboratory features | Family history (Consanguinity/siblings affected) | Initial Diagnosis | Molecular details | Treatment details | Follow-up duration and outcomes |
|--------------------------------|--------------------------|------------------|---------------------|-----------------------------------------------|------------------|-----------------|-----------------|-----------------------------|
| Pt. 7 (10 y/F) (19) | 0.91 y | Fever<br>Failure to thrive, Deforming inflammatory arthritis with contractures of small and large joints<br>ILD, corneal<br>Opacities in right eye | CRP: 97.23 mg/L<br>ESR: 120 mm/h<br>CT chest:ILD<br>RA factor: positive<br>ANA: 4+ RIM<br>lgG: >2.535 (540–1,610)<br>lgA: <436 (70–250)<br>C3: 166 mg/dl (89–187)<br>C4: 20 mg/dl (16–38)<br>Anti ds-DNA: 10.8 IU/ml (<25- Negative)<br>Serum IL-6: 3,700 pg/ml<br>Serum IL-10: 13,900 pg/ml<br>Interferon levels elevated | JIA, COPA<br>Brother and Father affected (Pt. 8 and Pt. 9) | TMEM173 exon5; c.463G>A; p.Val155Met<br>Homozygous missense variation | Previously reported: Yes | CS, MTX, AZR, Naproxen, HCQ | Alive |
| Pt. 8 (3 y/M) (19) | 2 y | Fever<br>Polyarthitis (bilateral knee, small joints of the hands)<br>Rash<br>ILD | CRP: 12.98 mg/L<br>ESR: 108 mm/h<br>CT chest:ILD<br>RA factor: negative<br>ANA: 2+ Speckled<br>IL-6: 3,500 pg/ml<br>IL-10: 14123 pg/ml<br>Interferon levels elevated | B/o Pt. 7 | TMEM173 exon5; c.463G>A; p.Val155Met<br>Homozygous missense variation | Same as Pt. 7 | AZR, MTX | Well |

(Continued)
| Center                      | Patient (Age at diagnosis/ Sex) | Age of onset of symptoms | Clinical features                                                                 | Laboratory features                                                                 | Family history (Consanguinity/ siblings affected) | Initial Diagnosis | Molecular details | Treatment details | Follow-up duration and outcomes |
|-----------------------------|---------------------------------|--------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------|-------------------|------------------|------------------|-------------------------------|
| Pt 9 (4y/-) (19)            |                                 |                          | • Deforming inflammatory polyarthritis involving small and large joints           | ESR: 12 mm/h<br>RA Factor: 6.49 mg/L<br>ANA (IF): 3 +<br>CT chest: Emphysematous changes and interstitial thickening in bilateral lungs consistent with ILD | F/o Pt. 7<br>TMEM173 exon5; c.463G>A; p.Val155Met<br>heterozygous missense variation | RA                | -                | -                | -                |

**Spondyloenchondrodysplasia (SPEND) (n = 2)**

| SGPGI | Pt. 10 (15 y/F) | 13 y | • Fever<br>• Seizure<br>• Stroke<br>• Optic atrophy<br>• Hypertensive<br>• Short stature | MR brain: Basal ganglion calcification<br>Renal biopsy: IgA nephropathy<br>ANA–Positive<br>Anti dsDNA: 67.5 IU<br>C3/C4: 105 mg/dL/29.6 mg/dL<br>IgG: 3.590 mg/dl<br>IgA: 621 mg/dl<br>IgM: 60.9 mg/dl | No | SLE | ACP 5 exon 3; c.550C>T; p.Gln184*<br>exon 4; c.740T>G; p.Leu247Arg | HCQs, antihypertensive NA drugs |

| Lilavati Hospital | Pt. 11 (4y/F) | 1y | • Fever<br>• Bleeding (Skin, mucosal and intracranial)<br>• Anemia<br>• Facial dysmorphism (delay in motor and cognitive milestones, fronto-parietal bossing, hypertelorism, low set ears) | X-ray wrist: metaphyseal dysplasia<br>C T brain: Symmetrical bilateral basal ganglion calcifications and gliotic area noted in left Parieto-Temporal area<br>Bone marrow biopsy: hypercellular marrow with erythroid and megakaryocytic hyperplasia. Increased bone marrow fibrosis<br>DCT ICT: strongly positive multiple antibodies<br>Cold agglutinin; positive | No | Early onset Immune thrombocytopenia<br>ACP 5 exon 1; c.136delc; p.R46Gfs*24<br>Homzygous nucleotide deletion<br>Parents heterozygous for the same variant | Multiple packed cell transfusions and platelet transfusions<br>IVg, CS, dapsone, cyclosporine | Doing well |
### Cryopyrin-Associated Periodic Syndromes: CAPS

In this cohort we report seven patients with CAPS caused by mutations in NLR family pyrin domain containing 3 (NLRP3) gene. All patients had been symptomatic since early infancy but there were significant delays in diagnosis. Age at diagnosis ranged from 15 months to 13 years. Most of these patients were initially diagnosed as JIA. Seven patients had classical phenotype of NOMID with infantile onset of fevers, urticarial rash, arthritis, and progressive deformities with bony overgrowths (Figure 4). Sensory neural hearing loss and headache was found in only1 patient. Of the seven patients, pathogenic variants in NLRP3 gene were identified in four patients (patient no. 21–23, 27) while no mutation could be identified in patient no 24 on exome sequencing. Molecular studies of two patients (patient 25, 26) are awaited. Three patients (patient no 21,22, and 23) had developed amyloidosis when by the time diagnosis of CAPS was established and two patients (patient no 21 and 23) succumbed to their illness. Drugs used for treatment included corticosteroids, thalidomide and colchicine as anti-interleukin 1 (anti-IL1) therapy was not easily accessible. 4/7 patients with CAPS died while 3 were alive at the time of this report. Patient no. 22 has been on thalidomide for 12 years which has resulted in normalization of inflammatory parameters but she continues to have significant growth retardation, deformities, and intermittent headaches.

### NLRP12

Variants in NLRP12 gene were identified in two patients (patient no 28, 29). Both children were symptomatic since early infancy. Patient no. 28 had presented with recurrent episodes of fever, and infections (skin and subcutaneous abscess, diarrhea, meningitis, pneumonia), arthritis, sensorineural hearing loss and hepatosplenomegaly while patient no. 29 in addition had urticarial rash, pestular skin lesions, and lymphadenopathy. Heterozygous mutation in exon 3 in NLR family pyrin domain containing 12 (NLRP12) gene was identified. Corticosteroids were used for treatment in patient 28 and is currently well.

### FMF

Clinical profile of patients (Patient no 30, 31) with variants in MEFV gene is summarized in Table 2. Patient no. 30 had presented with periodic fever, rash, and abdominal pain. Targeted panel revealed variants of unknown significance in MEFV gene and Phospholipase C Gamma 2 (PLCG 2) gene. The patient is doing well on colchicine.

Nine months old boy (patient 31) had presented with recurrent oral ulcers. In view of family history of oral ulceration exome sequencing was performed. Heterozygous isense mutation in MEFV gene was identified. Symptomatic improvement has been noted after initiation of colchicine.

### APLAID

Clinical profiles of patients no. 32, 33 with PLCG2 variants are summarized in Table 2. Patient no. 32 had erythematous macular
rash (Figure 5), large joint arthritis, episodes of intussusception along with recurrent sinopulmonary infections. A de-novo heterozygous missense mutation in exon 22 of PLCG2 gene that resulted in substitution of serine by asparagine at codon 798 (pAsn798Ser), was validated using Sanger sequencing. The Asn798Ser variant has a minor allele frequency of 0.08, 0.07, and 0.16% in the 1,000 genomes, EXAC and internal databases, respectively. The in-silico predictions of the variant were found damaging by PolyPhen-2 (HumDiv), damaging by Sorting Intolerant from Tolerant (SIFT), likelihood ratio test (LRT) and Mutation Taster 2.

Patients no. 33 had scaring photosensitive rash and a provisional diagnosis of Kindler syndrome was made (Mahajan et al. manuscript in submission). He was also detected to have same mutations in PLCG2 gene as patient no. 31. Both these patients were unrelated and belonged to different ethnic backgrounds. They had multiple relapses and both succumbed to their illness.
CLINICAL PROFILE OF PATIENTS WITH NON-INFLAMMASOME RELATED CONDITIONS

Thirty patients (38%) in our cohort were grouped under non-inflammasome related conditions that included TNF receptor-associated periodic syndrome (TRAPS) (three patients); Deficiency of the Interleukin 1 Receptor Antagonist(DIRA) (two patients); Pyogenic sterile Arthritis, Pyoderma Gangrenosum, Acne syndrome (PAPA) (one patient); A20 haploinsufficiency (four patient); CCA-adding transfer RNA nucleotidyl transferase (TRNT1) (two patients); Caspase recruitment domain-containing protein 14 (CARD 14) (one patients); and Laccase Domain Containing 1 (LACC1) (three patients from one family) (Table 3). Patients with Blau syndrome (14 patients are not being presented in this paper (Suri et al., manuscript in submission). Patient with LACC1 has also been reported previously (27) (Table 3).

TRAPS

Patient no. 34 had recurrent episodes of fever lasting for 2–3 weeks every 3–4 months with rash since 18 months of age. These episodes were associated with pain abdomen, myalgias, arthritis, periorbital edema (Figure 6), and subcutaneous swellings. She had received multiple courses of antimicrobials in view of marked polymorphonuclear leukocytosis. Her father was also symptomatic and used to have fever and intermittent subcutaneous swelling and rash. Father was diagnosed to have acute rheumatic fever in childhood. In view of periodic fever, with systemic manifestations and family history suggestive of autosomal dominant disorder, diagnosis of TRAPS was proffered and confirmed on exome sequencing. She was initially managed with corticosteroids followed by injection etanercept. She remains well at follow up.

A 4-years old girl (patient no 39) had been unwell for 2.5 years associated with pain abdomen, myalgias, arthritis, periorbital edema (Figure 6), and subcutaneous swellings. She had received multiple courses of antimicrobials in view of marked polymorphonuclear leukocytosis. Her father was also symptomatic and used to have fever and intermittent subcutaneous swelling and rash. Father was diagnosed to have acute rheumatic fever in childhood. In view of periodic fever, with systemic manifestations and family history suggestive of autosomal dominant disorder, diagnosis of TRAPS was proffered and confirmed on exome sequencing. She was initially managed with corticosteroids followed by injection etanercept. She remains well at follow up.

DIRA

Patient no 37 as has been previously reported (26), was the first Indian patient with large deletion in Interleukin 1 Receptor Antagonist (IL1RN) gene. She is doing well on Anakinra at 6 years of follow-up supported by National Institutes of Health, USA.

Patient no 38 had presented at day 7 of life with paucity of movement of both upper limbs. Inflammatory parameters were increased with sterile blood cultures. X-rays showed bilateral humerus, rib and clavicular involvement. He was treated with oral prednisolone 2 mg/Kg with slow taper over 4 months. He responded dramatically and bone lesions healed. He developed pustules at follow up. Deletion in IL1RN gene as in patient no 37 was not detected on Western blot analysis. Results of whole exome sequencing are awaited. He is currently doing well and off corticosteroids. However, ESR remains elevated.

PAPA Syndrome

A 4-years old girl (patient no 39) had been unwell for 2.5 years when she presented with periodic fevers associated with painful oral ulcers, abdominal pain with hematochezia and colitis. Over the years, she developed multiple pyoderma gangrenosum lesion over extremities, angle of mouth and gluteal region that caused complete destruction of left cheek and lower lip. The lesion were difficult to heal and resulted in fistulae formation. She was initially suspected to have inflammatory bowel disease and oral prednisolone and azathioprine were initiated. Injection infliximab (3 doses) were also commenced. There was partial response in skin lesions and colitis initially. However, lesions reoccurred, and she succumbed to her illness.

A20 Haploinsufficiency

Patient 40 was 2 years old when she had presented with recurrent oral ulcers and genital ulcers (Figure 7). She had colitis, refractory ulcers requiring repeated hospitalization. Markers of inflammation were elevated, and Human Leucocyte Antigen 51 (HLA B 51) allele was detected. Considering a possibility of Bechet’s disease, she was commenced on corticosteroid and azathioprine. At 5 years, she was readmitted with persistent
| Center       | Patient (Age of diagnosis (years)/sex) | Age of onset of symptoms (months) | Clinical features                                                                 | Laboratory features                          | Family history (Consanguinity/Family history) | Initial diagnosis                                                                 | Molecular details                                                                 | Treatment details | Follow-up duration and outcomes |
|--------------|----------------------------------------|----------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------|------------------|----------------------------------|
| Hyper IgD Syndrome/Mevalonate Kinase Deficiency (MVK) (n = 8) |
| PGIMER       | Pt. 13 (1.33 y/M)                       | 2 months                         | Fever, Jaundice, Cholestatic, hepatosplenomegaly, Failure to thrive               | CRP: 290 mg/L ESR: 110 mm/hr                  | Yes (Younger brother of patient 14)           | Neonatal cholestasis with sepsis                                                      | MVK exon 9; c.803 T>C; p.Ile268Thr exon 10; c.976G>A; p.Gly326Arg Missense (phase unknown) | Thalidomide      | Alive intermittent episodes of fever present |
|              | Pt. 14 (4.5 y/M)                       | 2 months                         | Fever, Jaundice, Anemia, generalized lymphadenopathy, hepatosplenomegaly, Failure to thrive | CRP: 56 mg/L ESR: 38 mm/hr                    | B/o Pt 13                                     | Sepsis                                                                              | MVK exon 9; c.803 T>C; p.Ile268Thr exon 10; c.976G>A; p.Gly326Arg Missense | Thalidomide      | Alive and well                   |
|              | Pt. 15 (3.5 y/F)                       | 6 months                         | Polyarthritis (wrist, elbows, knee), abdominal pain, Diarrhea, colitis, Anemia, generalized lymphadenopathy, Global developmental delay | CRP: 160 mg/L ESR:109 mm/h Bone marrow biopsy: Dyserthropoiesis with lymphoid aggregates Gut biopsy: acute on chronic inflammation IgG: 2,079 mg/dL IgA: 303 mg/dL | 3rd degree consanguinity, no similar illness in family | JIA/Blau/IBD arthritis                                                                | MVK exon 6; c.546G>T; p.Leu182Phe Homozygous, Missense            | CS, MTX, AZA     | Alive and well                   |
|              | SGPGI                                  |                                 |                                                                                   |                                               |                                               |                                                                                     |                                                                     |                  |                                   |
|              | Pt. 16 (15 y/M)                        | 3 months                         | Fever, Rash, Arthralgia, Pleuritis, Peritonitis, Hepatosplonemegaly, generalized lymphadenopathy | CRP: 80 mg/L ESR: 90 mm/hr IgG: 1,465 mg/dL IgA: 1,166 mg/dL IgM: 58.6 mg/dL | Sibling of Pt 17                             | AID ? HIGD syndrome                                                                | MVK Exon 11 c.1129G>A p.V3771                                      | NSAIDs           | Change in treatment: DMARDs stopped |
|              | Ref (14)AM                             |                                 |                                                                                   |                                               |                                               |                                                                                     |                                                                     |                  | NA                               |
|              | Pt. 17 (11 y/M)                        | 2 months                         | Fever, Rash, Arthralgia, Hepatosplonemegaly, generalized lymphadenopathy, Peritonitis, adhesions on laparotomy | IgG:1377mg/dL IgA:633mg/dL IgM:119.1mg/dL     | Sibling of Pt 16                             | AID ? HIGD syndrome                                                                | MVK Exon 11 c.1129G>A p.V3771                                      | NSAIDs           | Change in treatment: DMARDs stopped |

(Continued)
| Center          | Patient (Age of diagnosis (years)/sex) | Age of onset of symptoms (months) | Clinical features                                      | Laboratory features                          | Family history (Consanguinity/Family history) | Initial diagnosis | Molecular details | Treatment details | Follow-up duration and outcomes |
|----------------|---------------------------------------|-----------------------------------|-------------------------------------------------------|----------------------------------------------|--------------------------------------------|------------------|------------------|-------------------|------------------------|
| BJWHC          | Pt. 18 (3 y/M)                         | 12 months                         | Fever Petechial rash                                  | -                                            | -                                          | -                | -                | MVK exon 2; c.10G>T; p.Glu4Ter (this is novel) exon 11; c.1129G>A; p.Val377le Het/AR (this is already known as common Dutch founder variant) | NA            | Doing well       |
|                | Pt. 19 (0.91 y/M)                      | 15 days                           | Fever, Rash Failure to thrive                         | IgG: 2,400 mg/dL, IgA: 159 mg/dL, IgM: 341 mg/dL, CD3: 3,724, CD19: 1,375, CD56: 516 | No PID                                      | MVK Exon11: c.1097A>G, Asp366Gly Novel and homozygous Not published | CS            | NA               |
| CMC Vellore    | Pt. 20 (1 y/F)                         | NA                                | Recurrent infections, Fever, Anemia Failure to thrive | IgG: 520mg/dL, IgA: 43mg/dL, IgM: 39mg/dL, Tg and Ferritin: increased Fibrinogen: normal Coombs: 1+ NBET: normal | NA                                          | NA MVK Exon7: c.644G>A; p.Arg215Gin Homozygous | NA            | NA               |
| PGIMER         | Pt. 21 (10 y/F) (51)AM                 | 1 month                           | Recurrent urticarial rash, Arthritis (ankle and wrist), Hypertension, Conjunctivitis, Optic atrophy, nephrotic range anasarca, Proteinuria, Hypothyroidism, CSVT | CRP: 19.5 mg/L, ESR: 51 mm/hr Renal biopsy: AA Amyloidosis, IgG: 623 mg/dL; IgA: 253mg/dL IgM: 282 mg/dL | No Atypical nephrotic syndrome NLRP3 (exon 3; c.1055C > T; p.Ala352Val) Substitution | CS, thalidomide, enalpril, amlodipine | Died due to amyloid associated renal failure |
|                | Pt. 22 (13 y/F)                        | Infancy                           | Fever, Rash, Arthritis with bony overgrowth, Headache, Short Stature | CRP: 60 mg/L, ESR: 96 mm/hr FNAC, abdominal fat pad, amyloidosis | -                                           | Systemic JIA NLRP3 exon 3; c.913G>C; p.Asp305His | CS, thalidomide | Alive            |

Cryopyrin-Associated Periodic Syndromes (CAPS)/Muckle-Wells Syndrome (MWS)/Neonatal-Onset Mutsystem Inflammatory Disease (NOMID) (n = 7)
## TABLE 2 | Continued

| Center | Patient (Age of diagnosis (years)/sex) | Age of onset of symptoms (months) | Clinical features | Laboratory features | Family history (Consanguinity/Family history) | Initial diagnosis | Molecular details | Treatment details | Follow-up duration and outcomes |
|--------|--------------------------------------|----------------------------------|------------------|--------------------|---------------------------------------------|-------------------|------------------|------------------|----------------------------------|
|        | Pt. 23 (11 y/M)                        | NA                               | Fever, Arthritis, Amyloidosis, renal failure | CRP: 58 mg/L ESR: 89 mm/hr FNAC, abdominal fat pad, renal biopsy, amyloidosis | -                | Systemic JIA | NLRP3 exon 3; c.1792C>T; p.Thr349Ile | CS                | Died due to amyloid associated renal failure |
|        | Pt. 24 (6.5 y/M) (32) AM               | 18 months                        | Fever, Erythematous macular non itchy rash, later painful nodular, Seizures with meningitis, SNHL | CRP: 65 mg/L ESR: 96 mm/hr Skin panniculitis, non specific perivascular dermatitis MR brain: Bilateral Bilateral cerebellar atrophy with mild hydrocephalus | No               | Tubercular meningitis | NLRP3 genetic screening negative for all exons | CS, thalidomide | Died |
| SGPGI  | Pt. 25 (4 y/F)                         | Since birth                      | Fever, Arthritis, Urticaria, Knee flexion contractures, Short stature, Hepatosplenomegaly | CRP: 11.7 mg/L ESR: 30 mm/hr | No               | Oligo JIA, NOMID | Mutation screening under process | CS                | Doing well |
|        | Pt. 26 (5 y/M)                         | Since birth                      | Fever, Arthritis, Urticaria, Lymphadenopathy, hepatosplenomegaly | CRP: 12 mg/L ESR: 90 mm/h IgG: 1,590 mg/dL IgA: 275 mg/dL IgM: 109 mg/dL IgE: 409.8 mg/dL | No               | NOMID | Mutation screening under process | CS                | Doing well |
| BJWHC  | Pt. 27 (1.33 y/M)                      | D1 of life                       | Fever, Urticarial rash, Hepatosplenomegaly, Hypertelorism, Macrophaly, Delay in cognitive milestones | CRP: 10 mg/L ESR: 140.5 mm/h MRI brain: Mild cerebral atrophy with dilated lateral ventricles and cisterns IgG: 1,472 mg/dL IgA: 124 mg/dL IgM: 181 mg/dL IgE: 785 mg/dL | No               | AID | NLRP3 exon 4; c.2265G>A/G->C; p.Gly755Arg | CS, NSAIDs | Died |

### NLR Family Pyrin Domain containing 12 (NLRP12) (n = 2)

| Center | Patient (Age of diagnosis (years)/sex) | Age of onset of symptoms (months) | Clinical features | Laboratory features | Family history (Consanguinity/Family history) | Initial diagnosis | Molecular details | Treatment details | Follow-up duration and outcomes |
|--------|--------------------------------------|----------------------------------|------------------|--------------------|---------------------------------------------|-------------------|------------------|------------------|----------------------------------|
| SGPGI  | Pt. 28 (4 y/F)                        | Since birth                      | Fever, Diarrhea, Pneumonia, Arthritis | CRP: 54 mg/L ESR: 54 mm/hr | No               | PID | NLRP12 exon 9; c.2935A>G; p.Ser979Gly published | CS                | NA |

(Continued)
### TABLE 2 | Continued

| Center          | Patient (Age of diagnosis (years)/sex) | Age of onset of symptoms (months) | Clinical features                                                                 | Laboratory features                                                                 | Family history (Consanguinity/Family history) | Initial diagnosis | Molecular details | Treatment details | Follow-up duration and outcomes |
|-----------------|----------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------|-------------------|-------------------|-------------------|-----------------------------|
|                 |                                        |                                   | • Cervical lymphadenopathy and hepatosplenomegaly, Skin pustules, subcutaneous abscess, Meningitis, SNHL | Gut biopsy: cryptitis with occasional crypt distortion NBT: Normal CD3, CD19, CD56: Normal |                                | -                | AID               | CS                | Well                        |
|                 | Pt. 29                                 | 1 month                           |                                    | CRP: 72 mg/L ESR: 103 mm/hr USG: synovial thickening of joint and both radiocarpal joints. C3/C4: 1.73 mg/dL /0.25 mg/dL |                                |                                |                   |                   |                                |
|                 | (1 y/M)                                |                                   |                                    |                                                                                   |                                |                                |                   |                   |                                |
| Familial Mediterranean Fever (FMF) (n = 2) |                                |                                   |                                    |                                                                                   |                                |                                |                   |                   |                                |
| BJWHC           | Pt. 30                                 | 4 months                          | Fever Irritability Maculopapular rash Recurrent abdominal pain Hepatomegaly        | CRP: 39 mg/L ESR: 53 mm/hr CD3: 4,084 CD19: 2,106 CD56: 128 NBT: 97%                  |                                | No               | AID               | Plcg2             | Colchicine Doing well |
|                 | (0.91 y/F)                             |                                   |                                    |                                                                                   |                                |                                |                   |                   |                                |
|                 |                                        |                                   |                                    |                                                                                   |                                |                                |                   |                   |                                |
| PGIMER          | Pt. 31                                 | 9 months                          | Oral ulcers                        | CRP: 1.87 mg/L ESR: 37 mm/hr TH17/STAT3: reduced IgE: Normal NBT: Normal CD3, CD19, CD56, CD4, CD8: Normal |                                | N/Yes (oral ulcers in father; Not Screened) PID (TH17/PSTAT1 defects) | MEFV exon 10: c.2177T>C; p.Val766Ala heterozygous, missense. This is a non-confirmatory variant as per new Eurofever/PRINTO classification criteria | Fluconazole Colchicine | Alive |
|                 | (1.66 y/M)                             |                                   |                                    |                                                                                   |                                |                                |                   |                   |                                |

(Continued)
| Center          | Patient (Age of diagnosis (years)/sex) | Age of onset of symptoms (months) | Clinical features                                                                 | Laboratory features                                                                                     | Family history (Consanguinity/Family history) | Initial diagnosis | Molecular details | Treatment details | Follow-up duration and outcomes |
|----------------|----------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------|-------------------|-------------------|-------------------------------|
| PGIMER         | Pt. 32 (9 y/F)                          | 24 months                         | Generalized Erythematous macular rash, bilateral knee and elbow arthritis, two episodes of intussception, otitis media | HRCT: bilateral hyper inflamed lung with fibrotic changes Skin Biopsy: non-specific perivascularitis with no immune deposits | ANA: 2+ speckled and nucleolar C3/C4: 73 mg/dL/ <8mg/dL CH50: 166% (69–129) IgG: 1,663 mg/dL/540–1,610 IgA: >594mg/dL (50–240) IgM: 117 mg/dL (50–180) IgE: >10,000 IU/mL CD3: 5.18 (5–78) CD19: 40.89 (10–31) CD56: 3.11 | Younger male sibling expired at 9 months, diarrhea, necrotic skin rash | SLE               | PLCG2 exon 22; c.2393 A>G; pAsn798Ser heterozygous, missense | CS, thalidomide, AZA Died                                                                 |
| Pt. 33 (3 y/M) | 4 months                               |                                   | Fever, Rash (multiple supportive lesions, erythematous plaques pustular lesions, alopecia(s) along with scars Photosensitivity Flexural contractures at small joints of hand, claw hand Bilateral corneal epithelial defect with corneal ulcers and corneal opacity Phimosis | CRP: 70 mg/L ESR: 100 mm/hr Skin Biopsy: Epidermis shows hyperkeratosis, focal neutrophilic crust over stratum corneum, basal cell vacuolation, perivascular infiltrates | ANA: Negative IgA: >595 mg/dL IgM: 89 mg/dL IgE: 8,856 mg/dL CD3/CD19/CD56: normal NBT /TH17/STAT3: normal | No                | Kindler syndrome, hyper IgE syndrome | PLCG2 exon 22; c.2393 A>G; pAsn798Ser heterozygous, missense | CS, MTX, IVIg Died                                                                 |
headache, blurring of vision and relapse of oro-genital ulcers. She had papilledema and magnetic resonance imaging (MRI) of brain revealed type 2 Arnold Chiari malformation. When younger brother also developed recurrent oral ulcers, genetic studies were performed in the index patient and targeted panel revealed a novel variant in Tumor necrosis factor alpha-induced protein 3 (TNFAIP3) gene (Table 3). She is doing well on follow up. Mother is carrier for the same variant while the younger sibling does not carry this variant. Patient 41 had also presented with early onset inflammatory bowel disease and oral ulcers and a novel variant in TNFAIP3 gene was found.

**TRNT1 Deficiency**

Patient no. 44, had presented with recurrent fever, and diarrhea. Two elder brothers earlier had died. He was evaluated for primary immune deficiency and was noted to have pan hypogammaglobulinemia. A provisional diagnosis of X-linked agammaglobulinemia was made and intravenous immunoglobulin replacement initiated. Exome sequencing revealed a compound heterozygous mutation in exon 2 of TRNT1 gene. Similarly, patient no. 48 also had recurrent infections, bronchiectasis and hypogammaglobulinemia.

**CARD 14:** Patient 46 had early onset difficult to treat psoriasis and was found to have mutations in CARD 14 gene.

**DISCUSSION**

SAID were first recognized in 1999 (4). Over the last two decades, knowledge and recognition of SAID has grown at an unprecedented speed and there have been a plethora of publications on this subject (3, 12, 13, 22). Significant improvement in understanding of genetic and pathogenic mechanisms of SAIDs has resulted in remarkable progress in their management. However, the data from India is limited (14–18, 26, 27, 33–40). There is no national registry for SAID and there is lack of knowledge on nationwide burden of these diseases. This manuscript is the first attempt to collate data from various centers involved in care of patients with SAID and highlight diagnostic difficulties, treatment, and outcomes of such patients in India.

SAID display wide range of clinical manifestations and can affect almost every organ system. They are uncommon and difficult to diagnose clinically. Overlapping clinical features of these disorders with other relatively common rheumatological disorders often lead to delay in diagnosis. At Chandigarh, we diagnosed our first child with NOMID in 2005. This child was being managed as systemic onset JIA for over 10 years. Similarly, patients with Blau syndrome were initially treated as JIA with uveitis, and patients with DADA2 as PAN. Other initial diagnosis included systemic lupus erythematosus, inflammatory bowel disease and Bechet's disease. With improved awareness amongst internists and pediatrician along with availability of affordable diagnostic techniques, these syndromes are now being suspected and diagnosed early.

Diagnosis of most SAID is based on clinical suspicion, family history and demonstration of elevated inflammatory parameters (ESR, CRP, serum amyloid A protein). Distinct interferon signatures and cytokine patterns may be helpful biomarkers to stratify and monitor patients. However, interpretation and standardization of these tests is difficult. Despite expansion of various laboratory investigations, these investigations are not yet available for clinical use in India. Genetic analysis is needed in all patients for confirmation of diagnosis. In the past, most genetic studies were performed in collaboration with international centers. In the last 5 years, molecular diagnostic techniques were established at PGIMER Chandigarh and National Institute of Immunohematology Mumbai, which are Indian Council of Medical Research (ICMR) recognized Centers for Advanced Research (CAR) in Primary Immune Deficiency Diseases. However, diagnostic facilities are still limited. At PGIMER, among SAID, we can perform Sanger sequencing for ADA2 and NOD2 genes. In recent years, NGS based targeted autoinflammatory panels are available in commercial laboratories, albeit expensive. Interpretation of data and functional validation of variants of unknown significance (VUS) detected remains a challenge.

Management of SAID is aimed at suppression of systemic inflammation. Colchicine and glucocorticoids have been traditionally used to treat SAID. However, with improved knowledge and understanding of pathogenic mechanisms of autoinflammation and availability of specific targeted immunotherapies, treatment strategies have been completely revolutionized (41, 42). Anti-IL-1 drugs (anakinra, canakinumab, and rilonacept), have become standard of care for most
| Center | Patient | Age of onset of symptoms | Clinical features | Laboratory features | Family history | Initial diagnosis | Molecular details | Treatment details | Follow-up duration and outcomes |
|-------|---------|--------------------------|------------------|--------------------|----------------|-----------------|------------------|------------------|----------------------------------|
| Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) \(n = 3\) |
| PGIMER Pt. 34 \(2.75\) y/F | 1 y 9 months | Periodic fever, Subcutaneous swellings, rash, periorbital edema, Recurrent episodes of abdominal pain | CRP: 41 mg/L ESR: 120 mm/hr IgG: 1,301 mg/dL, IgA: 135 mg/dL, IgM: 250 mg/dL NBT: Normal | Father affected; migratory lymphedema (same mutation) | Periodic fever | TNFRSF1A exon 3; c.215G>A p.Cys72Tyr previously unreported | CS, NSAID Change in treatment: etanercept | Alive |
| Pt. 35 \(45\) Y/F | Since adolescence | Fever, Arthralgia, Conjunctivitis, Pustular psoriasis (recurrent sterile pustular lesions) | CRP: 87 mg/L ESR: 65 mm/hr Skin biopsy: neutrophilic infiltrate in upper spinous and subcorneal layers | No | Pustular psoriasis | TNFRSF1A exon 9; c.902C>A p.Pro301His Missense Reported in gnomAD. Predicted to be pathogenic by polyphen and SIFT | CS, cyclosporine MTX | Died |
| Aster CMI Pt. 36 \(10\) y/M | 3 months | Recurrent fevers since early infancy (each episode for 3-4 weeks, febrile intervals up to 10 days), Rash over trunk and limbs, Limb pains and imp, Abdominal pain, Vomiting, Eye puffiness | CRP: 150 mg/L ESR: 120 mm/hr ANA: Negative | No | TRAPS | TNFRSF1A exon 9; c.146A>G; p.Tyr49Cys Previously reported | CS, antimicrobials Change in treatment: Etanercept – partial response Tocilizumab – responded | Alive and doing well |
| Deficiency of the interleukin-1 receptor antagonist (DIRA) \(n = 2\) |
| PGIMER Pt. 37 \(5\) months/F \(26\) | 21 days | Reduced movement and pain of left hip, left shoulder, right wrist, bilateral elbows since early infancy (multifocal osteitis), Pustules | CRP: 110.7 mg/L ESR: 113 mm/hr Bone scan: increased uptake in multiple joints (bilateral hip, shoulders, and sternoclavicular joints, lower ribs near costochondral junction and left elbow) X-ray: osteolytic lesions at humerus, left proximal femur, ribs and clavicle Bone biopsy: Bone inflammation | No | DIRA | IL1RN deletion, at chr2:113,865,011 Change in treatment done: Anakinra and chr2:113,887,227 homozygous 22,216bp deletion spans the first four exons of IL1RN, Parents carrier for same mutation \(NM\_173843\) Homozygous deletion Exon 1-4 deletion | Well |
| (Continued) |
### TABLE 3 | Continued

| Center               | Patient (age of diagnosis, years/sex) | Age of onset of symptoms | Clinical features                                                                 | Laboratory features                                                                                       | Family history | Initial diagnosis | Molecular details | Treatment details | Follow-up duration and outcomes |
|----------------------|---------------------------------------|--------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------|------------------|-------------------|-------------------|--------------------------|
| **Pyogenic Arthritis, Pyoderma gangrenosum and Acne (PAPA) (n = 1)** |                                       |                          |                                                                                   |                                                                                                           |                |                  |                   |                   |                          |
| PGIMER Pt. 39        | (5 y/F)                               | 2.5 y                    | Fever, Pyoderma gangrenosum, Colitis, Multiple abscess, Pus drainage, fistula, oral ulcers, pustules, Abdominal pain, Recurrent diarrhea | CRP: 101 mg/L ESR: 26 mm/hr Platelets: 964 x 10^9/L Colonoscopy: ileocecal valve thickened and distorted. Ileum shows active ulceration, cobble stone appearance, pseudo-polyp. Alteration of vascular pattern in cecum and ascending colon. Few active ulcers in hepatic flexure, transverse colon, recto sigmoid junction with pseudo-polyps. Impression: Crohn's disease or tuberculous colitis. Gut biopsy: Crohn's disease | -              | Crohn's disease | PSTPIP1 exon3; c.203C>T; p.Thr68Met Missense Place: Gasilini, Italy | ATT, CS, infliximab, AZA | Died                     |
| **A20 haploinsufficiency (TNFAIP3) (n = 4)** |                                       |                          |                                                                                   |                                                                                                           |                |                  |                   |                   |                          |
| PGIMER Pt. 40        | (6 y/F)                               | 6 M                      | Recurrent fever, Oro-genital ulcers, Ocular inflammation, blurring of vision, Headache, Papilledema, Abdominal pain, Arthritis, Colitis | CRP: 73.9 mg/L ESR: 26 mm/hr MR brain: type 2 Arnold Chiari malformation, HLAB51: positive ANA, ANCA: negative Gut Biopsy: no vasculitis | Younger brother has recurrent oral ulcers since 8 months age; Mother heterozygous for same variant | Behcet disease | TNFAIP3 exon 7; c.1504C>T; p.Arg502Trp Heterozygous missense | colchicine, AZA | Alive and well            |
| CMC Vellore Pt. 41   | (7 y/M)                               | NA                       | Autoinflammatory syndrome, Inflammatory ulcers duodenum to caecum, gastritis         | IgG: NA IgA: 579 mg/dL IgM: NA IgE: NA CD3: 487 CD19: 22 CD56: 410 | NA             | NA               | 7NFAP3 exon7; c.1316_1317del; p.Gly440ArgfsTer4 | NA                       | NA                       |                          |

(Continued)
### TABLE 3 | Continued

| Center       | Patient (age of diagnosis, years/sex) | Age of onset of symptoms | Clinical features                                      | Laboratory features | Family history | Initial diagnosis                                      | Molecular details | Treatment details | Follow-up duration and outcomes |
|--------------|---------------------------------------|--------------------------|--------------------------------------------------------|---------------------|----------------|------------------------------------------------------|------------------|-------------------|------------------------|
| CMC Vellore  | Pt. 42 (7y/M)                         | NA                       | • AIHA, • Skin rashes • Immune deficiency              | IgG: 2148mg/dL, IgA: 145mg/dL, IgM: 14mg/dL, IgE: NA Direct coombs test 3+, Ferritin normal. No increase in Double negative TCR αβ + T cells | NA              | NA                                                  | TNFAIP3 exon8; c.2036T->C; p.Ile679Thr Heterozygous VUS | NA               | NA                |
| CMC Vellore  | Pt. 43 (3y/M)                         | NA                       | Osteomyelitis/GD                                        | NA                  | NA             | TRNT1 deficiency (Sideroblastic anemia, immune deficiency, periodic fever, delay) (SIFD) (n = 2) | TRNT1 exon 2; c.143_144insTT p.Thr49Ter and exon 7;c.1043A->T p.Asp348Val compound heterozygous mutation | NA               | NA                |
| CMC Vellore  | Pt. 45 (5y/M)                         | NA                       | • Hypogammaglobulinemia • Bronchiectasis               | IgG: 478mg/dL, IgA: 31mg/dL, IgM: 50mg/dL, IgE: 22.8 mg/dL, CD3: 2,897, CD19: 96, CD56: 747 Elevated ferritin | NA              | NA                                                  | TRNT1 exon5; c.569G>T; p.Arg190Ile Homozygous | NA               | NA                |
| CMC Vellore  | Pt. 46 (8y/M)                         | NA                       | Psoriasis                                              | NA                  | NA             | CARD14 mediated psoriasis (CAMPS) (n = 1)            | CARD14 exon7; c.458G->C; p.Cys153Ser homozygous | NA               | NA                |

(Continued)
TABLE 3 | Continued

| Center | Patient (age of diagnosis, years/sex) | Age of onset of symptoms | Clinical features | Laboratory features | Family history | Initial diagnosis | Molecular details | Treatment details | Follow-up duration and outcomes |
|--------|--------------------------------------|--------------------------|-------------------|--------------------|------------------|-----------------|-----------------|-----------------|-----------------------------|
| **Laccase Domain Containing 1 (LACC1) defect (n = 3)** |
| PGIMER | Pt. 47 (5.75y/F) (27) | 9 M | Polyarticular joint disease. | X-ray: osteopenia, erosion of vertebrae without any platyspondyly | Sibling of Pt. 49 and 50 | Torg Winchester syndrome, Pseudorheumatoid chondrodysplasia and Familial inflammatory arthropathy | LACC1 exon4; c. 832G>C, p.Ala278Pro | Naproxen, CS, MTX | Doing satisfactory |
| | Pt. 48 (3y/F) (27) | 9 M | Polyarticular joint disease. | X-ray: osteopenia, erosion of vertebrae without any platyspondyly | Sibling of Pt. 48 and 50 | Similar to Pt 48 | Same as Pt 48 | Naproxen, CS, MTX | Doing satisfactory |
| | Pt. 49 (0.91y/F) (27) | 9 M | Polyarticular joint disease. | X-ray: ostopenia, erosion of vertebrae without any platyspondyly | Sibling of Pt. 48 and 49 | Similar to Pt 48 | Same as Pt 48 | Naproxen, CS, MTX | Doing satisfactory |

ANA, Antinuclear antibodies; Aster CMI, Aster CMI Hospital, Bengaluru, India; AZR, Azathioprine; CARD14, Caspase recruitment domain family member 14; CMC, Christian Medical College and Hospital, Vellore, India; CRP, C-reactive protein; COPA, Coatamer complex 1 protein alpha subunit; CS, Corticosteroids; CT, Computed tomography; CTA, Computed tomography angiography; ESR, Erythrocyte sedimentation rate; HCQS, Hydroxychloroquine; IL1RN, Interleukin 1 Receptor Antagonist; IgG, Intravenous immunoglobulin; JA, Juvenile idiopathic arthritis; LACC1, Laccase domain containing 1; MRI, Magnetic resonance imaging; MTX, Methotrexate; PGIMER, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India; PSTPIP1, Proline-serine-threonine phosphatase interacting protein 1; Reference of previously reported paper; TNFAIP3, TNF alpha induced protein 3; TNFRSF1A, TNF receptor superfamily member 1A; TRNT1, TRNA nucleotidyl transferase 1; Y, year.
inflammasomopathies. These agents successfully control inflammation and improve growth and quality of life. Other biologic agents used include anti-TNF drugs (etanercept), anti-IL-6 drugs (tocilizumab), and Janus kinase inhibitors (tofacitinib, baricitinib, and ruxolitinib). Treatment of SAID is extremely challenging in resource constrained settings. Anti-IL-1 drugs are not readily available in India and other developing countries. These drugs have to be imported on a “named-patient-basis” and are exorbitantly expensive. Some biosimilar molecules like anti-TNF (adalimumab, infliximab) and anti IL6 (tocilizumab) are available alternative therapies. Though these molecules are cost cheaper in India when compared to Western countries, yet they remain well beyond the scope of average Indian family. Thus, corticosteroids and other conventional immunosuppressive agents still form the mainstay of therapy. Patients often require higher doses as the disease progresses and they often develop corticosteroid related side effects. Off late, hematopoietic stem cell transplant (HSCT) is also emerging as a curative option for some SAID (43, 44). However, none of our patients received HSCT.

AID related morbidity and mortality continues to be high. In our cohort (8/49) have died at the time of analysis due to non-availability of treatment and development of complications. Amyloidosis had already developed in four patients at the time of diagnosis and it remains an important cause of death.

There are several limitations of this study. It is a case-based record review report from major primary immunodeficiency diseases centers across the country. Data from various individual rheumatology units could not be collated. Moreover, shared data were not uniform from all centers. Patients with unclassified SAID and patients in whom molecular diagnosis could not be established were excluded from the study.

This is a first comprehensive multicentric report of patients with SAID from India. Varied clinical and molecular spectrum has been reported. Considerable delays in diagnosis were recognized. Application of NGS based targeted panels and whole exome sequencing has helped in identifying known as well as novel gene defects. Establishment of diagnosis in a patient enabled early diagnosis...
of other family members and provided an opportunity for prenatal diagnosis. Although, ability to diagnose SAID has improved, non-availability of expensive immunotherapies remains a major drawback. In India corticosteroids and conventional immunosuppressive agents continue to remain corner stones for treatment. Lack of availability of targeted immunotherapies for treatment prevents the initiation of effective treatments that can change patients’ lives. SAID continue to result in significant morbidity and mortality.

To conclude, more efforts are needed to enhance awareness of autoinflammatory diseases among health care professionals and there is an urgent need to make life saving drugs universally available.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by Institute Ethics Committee, PGIMER, Chandigarh (Ref No: INT/IEC/2021/SPL-264). Written informed consent from the participants’ legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the minor(s)’ legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

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**DISCLOSURE**

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**AUTHOR CONTRIBUTIONS**

DS, AR, AJ, PV, AG, and RP: data collection, writing of initial draft, editing of manuscript at all stages of its production, patient management, and review of literature. DS, AR, AJ, PV, AG, RP, VJ, KA, RK, GA, AA, SP, FN, BG, EE, MD, PT, VG, AP, SB, and SK: data collection, management of patients, and review of final manuscript. AR, VJ, KA, RK, SP, FN, BG, and ES: genetic evaluation and data collection. MG, IC, AAdJ, and RG-M: genetic evaluation, review of final manuscript, and critical revision. AR, SB, SK, MG, IC, AAdJ, RG-M, and SS: genetic evaluation and review of the final manuscript. MH: performed ADA2 levels in patients with DADA two patients. DS, AR, and SS: patient management, review of literature, editing and critical revision of manuscript at all stages of its production, and final approval of manuscript. All authors contributed to the article and approved the submitted version.

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