



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). Type1 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

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

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). Euro fever 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 polygenic 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 I 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.

PATIENTS AND METHODS

Centers supported by the Foundation for Primary Immunodeficiency Diseases (FPID), USA, and other institutions involved in care of patients with Inborn Errors of Immunity (IEI) across India were contacted to share details of patients with SAID on a template designed by lead author (DS). Data including demographics, prominent clinical manifestations, laboratory investigations, molecular results, treatment regimens, and long-term outcomes were collated on predesigned Microsoft Excel sheet. Findings of radiology and histopathology were also recorded. Participating centers included Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, North India (52 patients); Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow, North India (25 patients); Christian Medical College, Vellore (12 patients), Bai Jerbai Wadia Hospital for Children (BJWHC), Mumbai, West India (10 patients); and ASTER CMI Hospitals, Bengaluru, South India (seven patients), Lilavati Hospital and Research Center, Mumbai, West India (one patient).

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 $>38^{\circ}\text{C}$) 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

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 (13 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 (*NOD2*) gene in patients suspected to have Blau syndrome (11/14 patients) and Adenosine deaminase 2 (*ADA2*) gene for 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 (12 patients, 15%); diseases affecting inflammasomes (21 patients, 26%);

and non-inflammasome related conditions (30 patients, 38%). Clinical details of patients with PFAPA (15 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); Spondyloenchondro 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 age in 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.

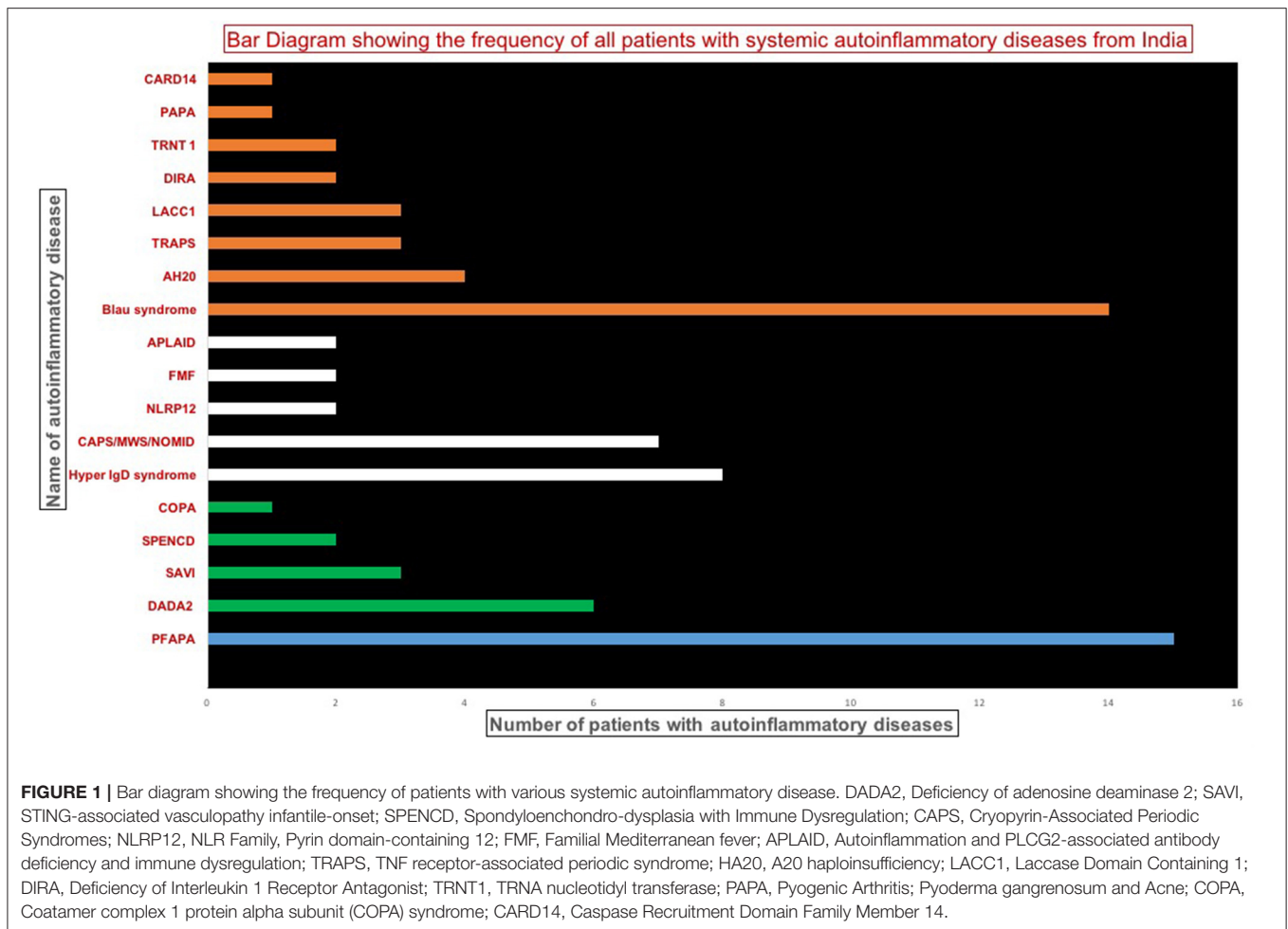
Patient no 3 was diagnosed to have central retinal artery occlusion. Inflammatory markers were persistently normal. His sister (patient two) was under treatment and follow up for PAN. She had presented with recurrent abdominal pain with perforation peritonitis and catheter angiography had revealed microaneurysms in mesenteric arteries and renal arteries (**Figure 2**). In view of family history DADA2 was suspected and mutation in *ADA2* gene was detected. Establishment of diagnosis led 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 (*ACP5*) 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 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
Deficiency of Adenosine Deaminase 2 (DADA2) ($n = 6$)									
PGIMER	Pt. 1 (31y/M)	3.3y	<ul style="list-style-type: none"> 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	<i>ADA2</i> 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 ant-TNF	34 years and doing well
	Pt. 2 (13 y/F)	5 y	<ul style="list-style-type: none"> 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 interobar 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	<i>ADA2</i> 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	<ul style="list-style-type: none"> 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	<i>ADA2</i> 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
SGPGI	Pt. 4 (17 y/M) (29)	5 y	<ul style="list-style-type: none"> Fever Vasculitic ulcers Seizures, Recurrent stroke with neurological deficits VIth Cranial Nerve palsy, median nerve neuropathy, GI bleed 	Skin Biopsy: Necrotizing cutaneous vasculitis	No	PAN	<i>ADA2</i> 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)

TABLE 1 | 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	<ul style="list-style-type: none"> Fever Ulcers and rash Recurrent stroke along with neurological deficits, mononeuritis multiplex, CRAO 	CRP: 5.11 mg/L ESR: 30 mm/h C3/C4: 129/32.3		PAN	<i>ADA2</i> exon 2; c.139G>C; p.Gly47Arg Homozygous missense variation Previously reported: Yes	CS, MMF Change in treatment: Stopped aspirin	doing well
Aster CMI	Pt. 6 (0.9 y/F) (29)	5 months	<ul style="list-style-type: none"> Fever Anemia generalized lymphadenopathy, splenomegaly 	CRP: 102 mg/L ESR: 155 mm/h Bone marrow: Normocellular bone marrow with trilineage hematopoiesis IgG: 1,640 mg/dL IgA: 101 mg/dL IgM: 96 mg/dL IgE: 3.7 mg/dL	No	-	<i>ADA2</i> exon 2; c.139G>C; p.Gly47Arg Homozygous missense variation Previously reported: Yes	Injection etanercept	Doing well
STING-associated vasculopathy with onset in infancy (SAVI) (n = 3)									
PGIMER	Pt 7 (10 y/F) (19)	0.91 y	<ul style="list-style-type: none"> Fever, Failure to thrive, Deforming inflammatory arthritis with contractures of small and large joints ILD, corneal Opacity in right eye 	CRP: 97.23 mg/L ESR: 120 mm/h CT chest: ILD RA factor: positive ANA: 4+ RIM IgG: >2,535 (540–1,610) IgA: 436 (70–250) C3: 166 mg/dl (89–187) C4: 20 mg/dl (16–38) Anti ds-DNA: 10.8 IU/ml (<25-Negative) Serum IL-6: 3,700 pg/ml Serum IL-10: 13,900 pg/ml Interferon levels elevated	Brother and Father affected (Pt. 8 and Pt. 9)	JIA, COPA	<i>TMEM173</i> exon5; c.463G>A; p.Val155Met heterozygous missense variation Previously reported: Yes	CS, MTX, AZR, Naproxen, HCQ	Alive
	Pt 8 (3 y/M) (19)	2 y	<ul style="list-style-type: none"> Fever Polyarthritis (bilateral knee, small joints of the hands) Rash ILD 	CRP: 12.98 mg/L ESR: 108 mm/h CT chest: ILD RA factor: negative ANA: 2+ Speckled IL-6: 3,500 pg/ml IL-10: 14123 pg/ml Interferon levels elevated	B/o Pt. 7	JIA, COPA	<i>TMEM173</i> exon5; c.463G>A; p.Val155Met heterozygous missense variation Same as Pt. 7	AZR, MTX	Well

(Continued)

TABLE 1 | 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)		<ul style="list-style-type: none"> Deforming inflammatory polyarthritis involving small and large joints ILD Peripheral vascular disease of bilateral lower limbs with guillotine amputation of right midfoot and 2nd toe in the year 2008 	ESR: 12 mm/h RA Factor: 6.49 mg/L ANA (IF): 3 + diffuse CT chest: Emphysematous changes and interstitial thickening in bilateral lungs consistent with ILD	F/o Pt. 7	RA	<i>TMEM173</i> exon5; c.463G>A; p.Val155Met heterozygous missense variation Same as Pt. 7	-	-
Spondyloenchondrodysplasia (SPENCD) (n = 2)									
SGPGI	Pt. 10 (15 y/F)	13 y	<ul style="list-style-type: none"> Fever Seizure Stroke Optic atrophy Hypertensive Short stature 	MR brain: Basal ganglion calcification Renal biopsy: IgA nephropathy ANA-Positive Anti dsDNA: 67.5 IU C3/C4: 105 mg/dL/29.6 mg/dL IgG: 3,590 mg/dl IgA: 621 mg/dl IgM: 60.9 mg/dl	No	SLE	<i>ACP 5</i> exon 3; c.550C>T; p.Gln184* exon 4; c.740T>G; p.Leu247Arg	HCQs, antihypertensive drugs	NA
Lilavati Hospital	Pt. 11 (4y/F)	1y	<ul style="list-style-type: none"> Fever Bleeding (Skin, mucosal and intracranial) Anemia Facial dysmorphism (delay in motor and cognitive milestones, fronto-parietal bossing, hyperteleorism, low set ears 	X-ray wrist: metaphyseal dysplasia CT brain: Symmetrical bilateral basal ganglion calcifications and gliotic area noted in left Parieto-Temporal area Bone marrow biopsy: hypercellular marrow with erythroid and megakaryocytic hyperplasia. Increased bone marrow fibrosis DCT ICT: strongly positive multiple antibodies Cold agglutinin: positive	No	Early onset Immune thrombocytopenia	<i>ACP 5</i> exon 1; c.136delc; p.R46Gfs*24 Homozygous nucleotide deletion Parents heterozygous for the same variant	Multiple packed cell transfusions and platelet transfusions IVIg, CS, dapsone, cyclosporine	Doing well

(Continued)

TABLE 1 | 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
Coatomer protein complex subunit alpha (COPA) defect (n = 1)									
PGIMER	Pt. 12 (11 y/M) (30)	5 Y	Polyarthritis, ILD	GRP: 32 mg/L ESR: 23 mm/h HRCT: ILD IgG: 1,453 mg/dL IgA: 131 mg/dL IgM: 135 mg/dL RA, CCP: Positive ANA: 3+ speckled ANCA: negative	Father died due to progressive lung disease	Poly JIA	COPA exon 9 (intron 9-10 junction) c.841C>T, p.Arg281Trp Novel heterozygous splice-site mutation Sangers (PG)	CS, MTX, HCQs	Alive

ACPF5, Acid phosphatase 5; ANCA, Anti neutrophil cytoplasmic antibody; ADA2, Adenosine deaminase 2; ANA, Antinuclear antibodies; anti TNF, Tumor necrosis factor; Aster CMI, Aster CMI Hospital, Bengaluru, India; AZR, Azathioprine; BJWHC, Bai Jiepai Wadia Hospital for Children, Mumbai, India; CMC, Christian Medical College and Hospital, Vellore, India; CRAO, Central retinal artery occlusion; CRP, C-reactive protein; CS, Corticosteroids; CT, Computed tomography; CTA, Computed tomography angiography; CYC, intravenous pulse cyclophosphamide; DCT, Direct Coombs test; DSA, Digital subtraction angiography; ESR, Erythrocyte sedimentation rate; HCQs, Hydroxychloroquine; HRCT, High resolution computed tomography GI, Gastrointestinal; ILD, Interstitial lung disease; IMA, Inferior mesenteric artery; JIA, Juvenile idiopathic arthritis; Lilavati Hospital, Lilavati Hospital and Research Center, Mumbai, India; LMWH, Low molecular weight heparin; MCA, Middle cerebral artery; MRI, Magnetic resonance imaging; MTX, Methotrexate; MMF, Mycophenolate mofetil; PAN, Polyarteritis nodosa; PGIMER, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India; RA, Rheumatoid arthritis; SGRPGI, Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGRPGI), Lucknow, India; SLE, Systemic lupus erythematosus; SMA, Superior mesenteric artery; TMEM173, Transmembrane protein 173; Y, years.

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 only 1 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, pustular 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 (*PLCG2*) 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 missense 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

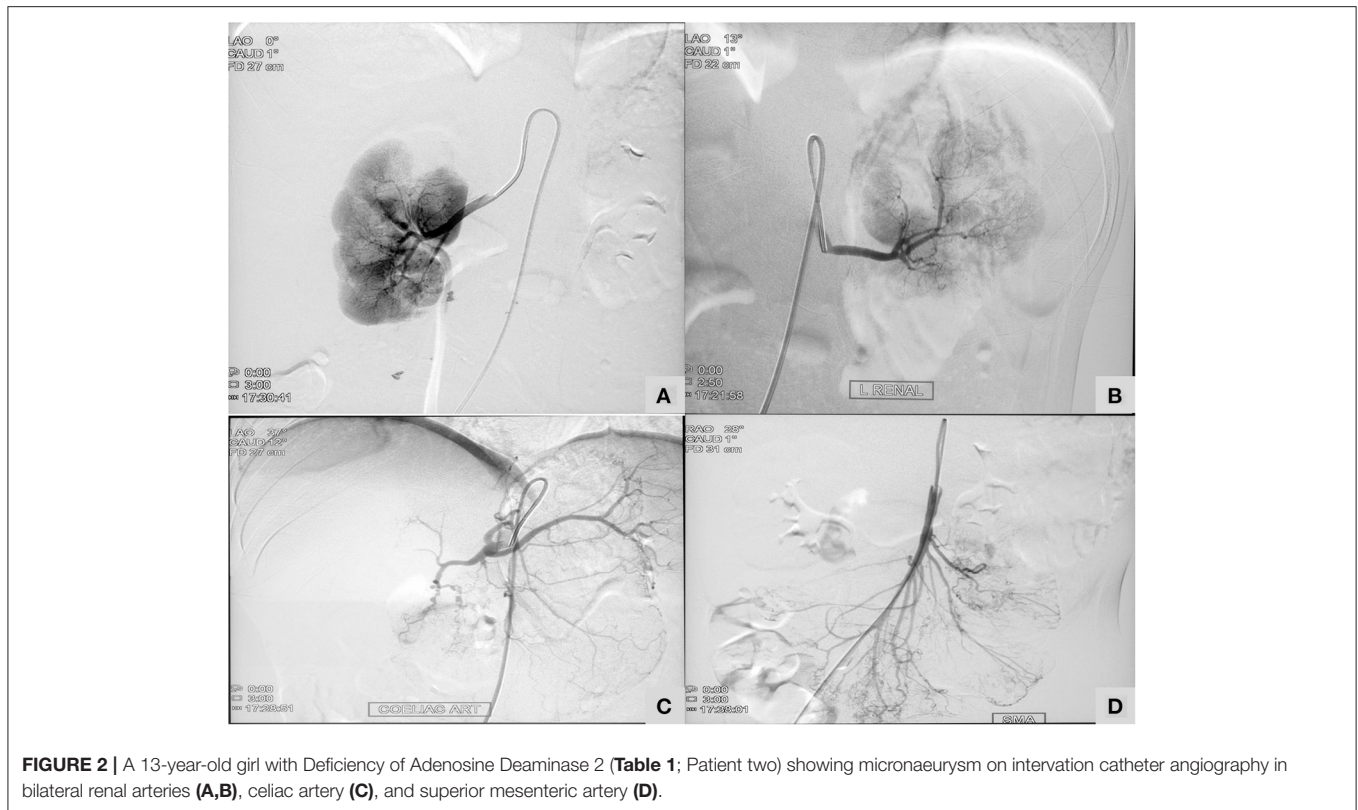


FIGURE 2 | A 13-year-old girl with Deficiency of Adenosine Deaminase 2 (Table 1; Patient two) showing microneurysm on intervention catheter angiography in bilateral renal arteries (A,B), celiac artery (C), and superior mesenteric artery (D).

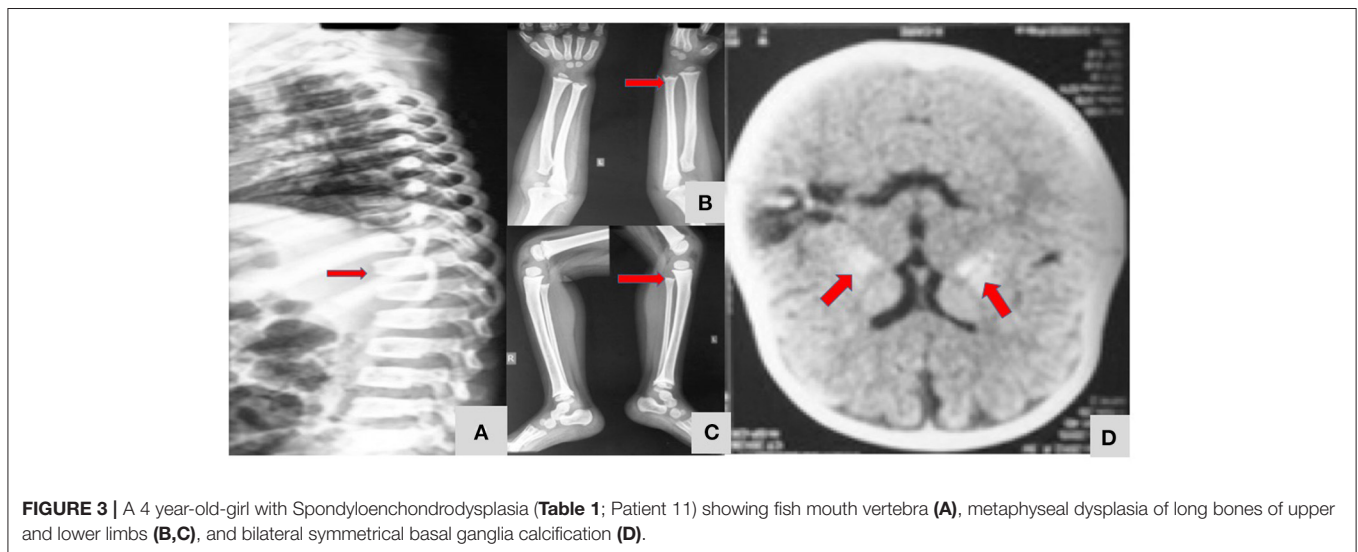


FIGURE 3 | A 4 year-old-girl with Spondyloenchondrodysplasia (Table 1; Patient 11) showing fish mouth vertebra (A), metaphyseal dysplasia of long bones of upper and lower limbs (B,C), and bilateral symmetrical basal ganglia calcification (D).

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 scarring 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.

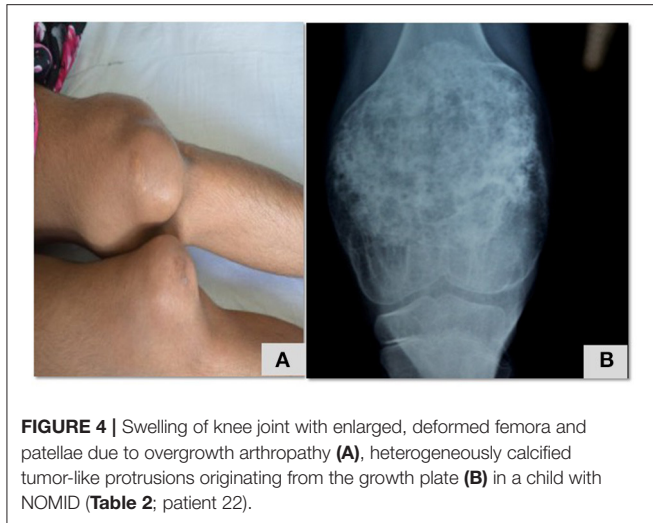


FIGURE 4 | Swelling of knee joint with enlarged, deformed femora and patellae due to overgrowth arthropathy (A), heterogeneously calcified tumor-like protrusions originating from the growth plate (B) in a child with NOMID (Table 2; patient 22).

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 patients); CCA-adding transfer RNA nucleotidyl transferase (TRNT1) (two patients); Caspase recruitment domain-containing protein 14 (CARD 14) (one patient); 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 45 years old female (patient no. 35) who had been under follow-up of Dermatology services was diagnosed to have pustular psoriasis since early adolescence. She would have intermittent flares with rash, fever and arthritis. Her disease

was refractory to methotrexate, cyclosporin and corticosteroids. In view of recurrent episodes of fevers, markedly elevated inflammatory parameters, sterile neutrophilic infiltrates on skin biopsy, a possibility of autoinflammatory disease was considered. Whole exome sequencing revealed variant in TNF Receptor Superfamily Member 1A (*TNFRSF1A*) mutation. She could not be initiated on biological agents due to financial constraints and succumbed to her illness 2 years after diagnosis was established.

A 10-year-old boy (patient no 36) had presented with high grade fever without focus. He reported having febrile episodes lasting for 3–4 weeks with variable afebrile periods since early childhood. These episodes were associated with rash over the trunk and limbs, myalgia and limp, abdominal pain, vomiting, and periorbital swelling. The inflammatory parameters were elevated and targeted panel for autoinflammatory diseases confirmed the diagnosis of TRAPS. The patient demonstrated partial response to etanercept which was changed to tocilizumab to which he responded well.

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

TABLE 2 | Clinical manifestations, molecular profile, treatment, and outcomes of patients with defect affecting the inflammasome ($n = 21$).

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	<ul style="list-style-type: none"> Fever Jaundice Cholestatic hepatosplenomegaly anemia Failure to thrive 	CRP: 290 mg/L ESR: 110 mm/hr	Yes (Younger brother of patient 14)	Neonatal cholestasis with sepsis	<i>MVK</i> 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	<ul style="list-style-type: none"> Fever Jaundice Anemia,generalized lymphadenopathy, hepatosplenomegaly Failure to thrive 	CRP: 56 mg/L ESR: 38 mm/hr	B/o Pt 13	Sepsis	<i>MVK</i> exon 9; c.803 T>C; p.Ile268Thr exon 10; c.976G>A; p.Gly326Arg Missense Same as Pt. 13	Thalidomide	Alive and well
	Pt. 15 (3.5 y/F)	6 months	<ul style="list-style-type: none"> Polyarthritis (wrist, elbows, knee), abdominal pain, Diarrhea, colitis Anemia, hepatosplenomegaly, generalized lymphadenopathy Global developmental delay 	CRP:160 mg/L ESR:109 mm/h Bone marrow biopsy: Dyserythropoiesis 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	<i>MVK</i> exon 6; c.546G>T; p. Leu182Phe Homozygous, Missense	CS, MTX, AZA	Alive and well
SGPGI	Pt. 16 (15 y/M) Ref (14)AM	3 months	<ul style="list-style-type: none"> Fever Rash Arthralgia Pleuritis Peritonitis Hepatosplenomegaly, 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 IgD: 938 mg/dL	Sibling of Pt 17	AID ? HIGD syndrome	<i>MVK</i> Exon 11 c.1129G>A p.V3771	NSAIDs Change in treatment: DMARDs stopped	NA
	Pt. 17 (11y /M) (14)AM	2 months	<ul style="list-style-type: none"> Fever Rash Arthralgia Hepatosplenomegaly, generalized lymphadenopathy Peritonitis, adhesions on laparotomy 	IgG:1377mg/dL IgA:633mg/dL IgM:119.1mg/dL IgD: 1363mg/dL	Sibling of Pt 16	AID ? HIGD syndrome	<i>MVK</i> Exon 11 c.1129G>A p.V3771	NSAIDs Change in treatment: DMARDs stopped	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
BJWHC	Pt. 18 (3 y/M)	12 months	Fever Petechial rash Recurrent cervical adenitis Sinusitis Hepatosplenomegaly	-	-	-	<i>MVK</i> exon 2; c.10G>T; p.Glu4Ter (this is novel) exon 11; c.1129G>A; p.Val377Ile Het/AR (this is already known as common Dutch founder variant)	NA	Doing well
	Pt. 19 (0.91 y/M)	15 days	<ul style="list-style-type: none"> • Fever • Rash • Failure to thrive • Dactylitis • Perianal abscess • Otitomycosis 	IgG: 2,400 mg/dL IgA: 159 mg/dL IgM: 341 mg/dL CD3: 3,724 CD19: 1,375 CD56: 516 NBT: Normal (98%)	No	PID	<i>MVK</i> Exon11; c.1097A>G; Asp366Gly Novel and homozygous Not published	CS	NA
CMC Vellore	Pt. 20 (1y/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+ NBT: normal	NA	NA	<i>MVK</i> Exon7; c.644G>A; p.Arg215Gln Homozygous	NA	NA
Cryopyrin-Associated Periodic Syndromes (CAPS)/ Muckle –Wells Syndrome (MWS)/Neonatal-Onset Mutisystem Inflammatory Disease (NOMID) (n = 7)									
PGIMER	Pt. 21 (10 y /F) (31)AM	1 month	<ul style="list-style-type: none"> • Recurrent urticarial rash • Arthritis (ankle and wrist) • hypertension, • conjunctivitis, • opticatrophy, • 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	<i>NLRP3</i> (exon 3; c.1055C > T; p.Ala352Val) Substitution	CS, thalidomide, enalapril, amlodipine	Died due to amyloid associated renal failure
	Pt. 22 (13 y/F)	Infancy	<ul style="list-style-type: none"> • Fever • Rash • Arthritis with bony overgrowth • Headache, • Short Stature 	CRP: 60 mg/L ESR: 98 mm/hr FNAC, abdominal fat pad, amyloidosis	-	Systemic JIA	<i>NLRP3</i> exon 3; c.913G>C; p.Asp305His	CS, thalidomide	Alive

(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
	Pt. 23 (11 y/M)	NA	<ul style="list-style-type: none"> • Fever • Arthritis • Amyloidosis, • renal failure 	CRP: 58 mg/L ESR: 89 mm/hr FNAC, abdominal fat pad, renal biopsy, amyloidosis	-	Systemic JIA	<i>NLRP3</i> 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	<ul style="list-style-type: none"> • 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	<i>NLRP3</i> genetic screening negative for all exons	CS, thalidomide	Died
SGPGI	Pt. 25 (4 y/F)	Since birth	<ul style="list-style-type: none"> • 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	Colchicine	Doing well
	Pt. 26 (5 y/M)	Since birth	<ul style="list-style-type: none"> • 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	Colchicine	Doing well
BJWHC	Pt.27 (1.33 y /M)	D1 of life	<ul style="list-style-type: none"> • Fever • Urticarial rash • Hepatosplenomegaly • Hypertelorism • Macrocephaly • 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	<i>NLRP3</i> exon 4; c.2263G>A/G>C; p.Gly755Arg	CS, NSAIDs	Died
NLR Family Pyrin Domain containing 12 (NLRP12) (n = 2)									
SGPGI	Pt. 28 (17)2 (4 y/F)	Since birth	<ul style="list-style-type: none"> • Fever • Diarrhea • Pneumonia • Arthritis 	CRP: 54 mg/L ESR: 34 mm/hr	No	PID	<i>NLRP12</i> 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
	Pt. 29 (1 y/M)	1 month	<ul style="list-style-type: none"> • Cervical lymphadenopathy and hepatosplenomegaly, • Skin pustules, subcutaneous abscess • Meningitis, SNHL • Fever • Urticarial rash, bullous eruptions over fingers, pustular skin lesion • Cervical and axillary lymphadenopathy 	Gut biopsy: cryptitis with occasional crypt distortion NBT: Normal CD3, CD19, CD56: Normal 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	-	AID	<i>NLRP12</i> exon3; c.779C>T; p.Thr260Met Heterozygous VUS Not published	CS	Well
Familial Mediterranean Fever (FMF) (n = 2)									
BJWHC	Pt. 30 (0.91y/F)	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	<i>PLCG2</i> exon 2;c.62C>T; p.Ala21Val het/AD/VUS <i>MEFV</i> exon 2; c.464G>C; p.Arg155Thr) Het/AD/VUS Not previously published. This is a non-confirmatory variant as per new Eurofever/PRINTO classification criteria	Colchicine	Doing well
PGIMER	Pt. 31 (1.66 y/M)	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)	<i>MEFV</i> exon 10; c.2177T>C; p.Val726Ala heterozygous, missense. This is a non-confirmatory variant as per new Eurofever/PRINTO classification criteria	Fluconazole Colchicine	Alive

(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
PLCG2 associated antibody deficiency and immune dysregulation (APLAID) (n = 2)									
PGIMER	Pt. 32 (9 y/F)	24 months	<ul style="list-style-type: none"> Generalized Erythematous macular rash, bilateral knee and elbow arthritis, two episodes of intussusception, otitis media Pneumonia, Recurrent vaginal bleeding Short stature 	HRCT: bilateral hyper inflated lung with fibrotic changes Skin Biopsy: non-specific perivasculitis with no immune deposits ANA: 2+ speckled and nucleolar C3/C4: 73 mg/dL/ <8mg/dL CH50: 166% (69–129) IgG: 1,683 mg/dL(540–1,610) IgA: >594mg/dL (50–240) IgM: 117 mg/dL(50–180) IgE: >10,000 IU/mL CD3: 51.8 (55–78) CD19: 40.89 (10–31) CD56: 3.11	Younger male sibling expired at 9 months, diarrhea, necrotic skin rash	SLE	<i>PLCG2</i> exon 22; c.2393 A>G; pAsn798Ser heterozygous, missense	CS, thalidomide, AZA	Died
	Pt. 33 (3 y/M)	4 months	<ul style="list-style-type: none"> Fever Rash (multiple supportive lesions, erythematous plaques pustular lesions, alopecia) 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 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	<i>PLCG2</i> exon 22; c.2393 A>G; pAsn798Ser heterozygous, missense	CS, MTX, IVIg	Died

AID, Autoinflammatory disorder; ANA, Antinuclear antibodies; AZR, Azathioprine; BD, Behcet disease; BJWHC, Bai Jerbai Wadia Hospital for Children, Mumbai, India; CMC, Christian Medical College and Hospital, Vellore, India; CRP, C-reactive protein; CS, Corticosteroids; CSVT, Cerebral sinovenous thrombosis; CT, Computed tomography; CTA, Computed tomography angiography; CYC, intravenous pulse cyclophosphamide; ESR, Erythrocyte sedimentation rate; FNAC, Fine needle aspiration cytology; HCQS, Hydroxychloroquine; Ig, Immunoglobulin; JIA, Juvenile idiopathic arthritis; MRI, Magnetic resonance imaging; MTX, Methotrexate; MMF, Mycophenolate mofetil; MVL, Mevalonate kinase; NBT, Nitroblue tetrazolium; NLRP3, NLR family pyrin domain containing 3; NLRP12, NLR family pyrin domain containing 12; PID, Primary immunodeficiency disorder; PGIMER, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India; PLCG2, Phospholipase C gamma 2; Ref, Reference of previously reported paper; SGPgI, Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGI), Lucknow, India; SNHL, Sensory neural hearing loss; TG, Triglycerides; Y, years.

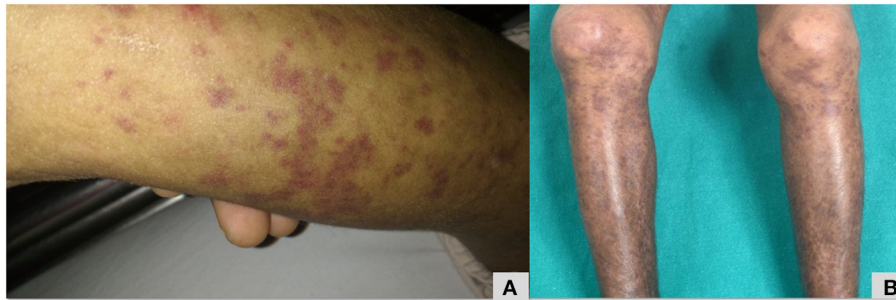


FIGURE 5 | Maculopapular erythematous rash over lower limb (A,B) that was initially diagnosed as Henoch Schlein purpura in a patient with PLCG2 (Table 2; patient no 32).

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 pediatricians 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 riloncept), have become standard of care for most

TABLE 3 | Clinical manifestations, molecular profile, treatment and outcomes of patients with non-inflammasome-related conditions ($n = 16$).

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
Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) ($n = 3$)									
PGIMER	Pt. 34 (2.75 y/F)	1 y 9 months	<ul style="list-style-type: none"> • 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 (270–1,580) IgA: 135 mg/dL (30–130) IgM: 250 mg/dL (50–220) NBT: Normal	Father affected; migratory lymphedema (same mutation)	Periodic fever	<i>TNFRSF1A</i> exon3; c.215G>A p.Cys72Tyr previously unreported	CS, NSAID Change in treatment: etanercept	Alive
	Pt. 35 (45 Y/F)	Since adolescence	<ul style="list-style-type: none"> • 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	<i>TNFRSF1A</i> exon9; 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	<ul style="list-style-type: none"> • Recurrent fevers since early infancy (each episode for 3-4 weeks, afebrile intervals up to 10 days), • Rash over trunk and limbs, • Limb pains and limp, • Abdominal pain • Vomiting • Eye puffiness 	CRP: 150 mg/L ESR: 120 mm/hr ANA: Negative	No	TRAPS	<i>TNFRSF1A</i> 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	<ul style="list-style-type: none"> • 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/h 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	<i>IL1RN</i> deletion, at chr2_hg19_113,865,011 and chr2_hg19_113,887,227 homozygous 22,216bp deletion spans the first four exons of <i>IL1RN</i> , Parents carrier for same mutation (NM_173843) Homozygous deletion Exon 1-4 deletion	Change in treatment done: Anakinra	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
	Pt. 38 (2.58 y/M)	7 days	Paucity of bilateral upper limb movements since day 7 of life Pustular lesions	CRP: 1.8 mg/L ESR: 8 mm/hr X-ray: bilateral humerus, clavicle and rib metaphyseal widening,	No	DIRA	Mutation for ILRN deletion as in patient 36 screened but not found	CS	Alive, healed lesions
Pyogenic Arthritis, Pyoderma gangrenosum and Acne (PAPA) (n = 1)									
PGIMER	Pt. 39 (5 y/F)	2.5 y	<ul style="list-style-type: none"> Fever Pyoderma gangrenosum Colitis Multiple abscess Pus drainage, fistula, oral ulcers, pustules Abdominal pain Recurrent diarrhea 	CRP: 101 mg/L ESR: 35 mm/hr Platelets: 964 × 109/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 ANA, ANCA: negative C3/C4: 182/23 IgG: 869 NBT, CD3: Normal	-	Crohn's disease	<i>PSTPIP1</i> exon3; c.203C>T; p.Thr68Met Missense Place: Gaslini, Italy	ATT, CS, infliximab, AZA	Died
A20 haploinsufficiency (TNFAIP3) (n = 4)									
PGIMER	Pt. 40 (6 y/F)	6 M	<ul style="list-style-type: none"> 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	<i>TNFAIP3</i> exon 7; c.1504C>T; p.Arg502Trp Heterozygous missense	colchicine, AZA	Alive and well
CMC Vellore	Pt. 41 (7 y/M)	NA	<ul style="list-style-type: none"> 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	<i>TNFAIP3</i> exon7; c.1316_1317del; p.Gly440ArgfsTer4 Heterozygous Novel Likely pathogenic	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	<ul style="list-style-type: none"> 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 $\alpha\beta$ + T cells	NA	NA	<i>TNFAIP3</i> exon8; c.2036T>C; p.Ile679Thr Heterozygous VUS	NA	NA
CMC Vellore	Pt. 43 (3 y/M)	NA	Osteomyelitis/CGD	NA	NA	NA	<ul style="list-style-type: none"> <i>TNFAIP3</i> exon7; c.1807G>A; p.Gly603Arg Heterozygous VUS 	NA	NA
TRNT1 deficiency (Sideroblastic anemia, immune deficiency, periodic fever, delay) (SIFD) (n = 2)									
ASTER CMI	Pt. 44 (3y/M)	6 months	<ul style="list-style-type: none"> Recurrent fever (each episode for 4-7 days and recur twice a month) Diarrhea Vomiting Panhypogammaglobulinemia 	IgG: 223 mg/dL IgA: 17mg/dL IgM: 24 mg/dL CD3: 77% (1927) CD19: 2.5% (62) CD56: 18% (460)	Two brothers had died within the first 2 years of life with recurrent fever	X-linked agammaglobulinemia	<i>TRNT1</i> exon 2; c.143_144insTT p.Thr49Ter and exon 7;c.1043A>T p.Asp348Val compound heterozygous mutation	Replacement IVIg	Doing well
CMC Vellore	Pt. 45 (5y/M)	NA	<ul style="list-style-type: none"> Hypogammaglobulinemia Bronchiectasis 	IgG: 478 mg/dL IgA: 31 mg/dL IgM: 50mg/dL IgE: 22.8 mg/dL CD3: 2,897 CD19: 96 CD56: 747 Elevated ferritin	NA	NA	<i>TRNT1</i> exon5; c.569G>T; p.Arg190Ile Homozygous	NA	NA
CARD14 mediated psoriasis (CAMPS) (n = 1)									
CMC Vellore	Pt. 46 (8 y/M)	NA	Psoriasis	NA	NA	NA	<i>CARD14</i> 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	<ul style="list-style-type: none"> • Polyarticular joint disease. • Joint symptoms with involvement of knee and ankle and rapidly progressed to involve small joints and cervical spine, multiple joint involvement, pain, deformities and contractures, bed bound, stunted, nail dystrophy, marked swelling, deformity of large and small joints 	X-ray: osteopenia, erosion of vertebrae without any platyspondyly RA Factor: positive	Sibling of Pt. 49 and 50	Torg Winchester syndrome, Pseudorheumatoid chondrodysplasia and Familial inflammatory arthropathy	LACC1 exon4; c. 832G>C, p.Ala278Pro Parents heterozygous for the same	Naproxen, CS, MTX	Doing satisfactory
	Pt. 48 (3y/F) (27)	9 M	<ul style="list-style-type: none"> • Polyarticular joint disease. • Joint symptoms with involvement of knee and ankle and rapidly progressed to involve small joints and cervical spine, multiple joint involvement, pain, deformities and contractures, bed bound, stunted, nail dystrophy, marked swelling, deformity of large and small joints 	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	<ul style="list-style-type: none"> • Polyarticular joint disease. • Joint symptoms with involvement of knee and ankle and rapidly progressed to involve small joints and cervical spine, multiple joint involvement, pain, deformities and contractures, bed bound, stunted, nail dystrophy, marked swelling, deformity of large and small joints 	X-ray: osteopenia, 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; IVIg, Intravenous immunoglobulin; JIA, 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 1 A; 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 main stay 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



FIGURE 6 | Unilateral periorbital edema without conjunctivitis noted in child with TRAPS during flares (Table 3; Patient no 34).

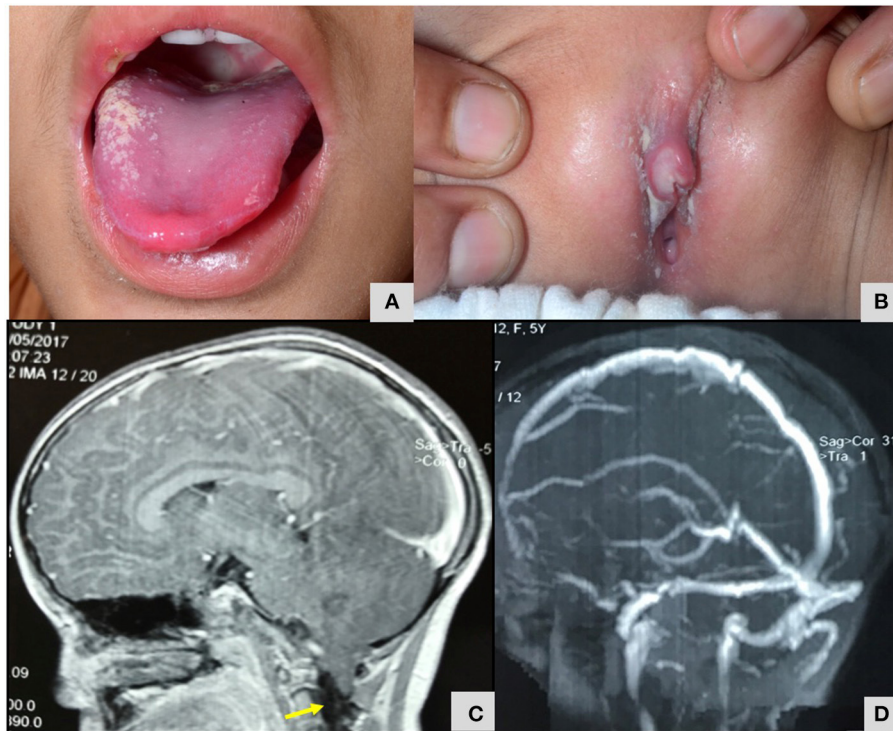


FIGURE 7 | (A,B) Oral cavity erythema and ulceration and genital ulcers in child with A20 haploinsufficiency (Table 3; Patient no 40). **(C)** MRI Brain T2 weighted sagittal section images demonstrating type 2 Arnold Chiari malformation (Table 3; Patient no 40). **(D)** MR venography of brain demonstrated normal flow and no evidence of cerebral sinus venous thrombosis (Table 3; Patient no 40).

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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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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