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Type I Interferonopathies in Childhood

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Type 1 interferonopathy is a novel context reflecting a group of inborn disorders sharing common pathway disturbances. This group of diseases is characterized by autoimmunity and autoinflammation caused by an upregulation of type 1 interferons (IFN)s due to certain genetic mutations. Several features are common in most of the diseases in this group, such as vasculitic skin changes, including chilblains, panniculitis, interstitial lung disease, basal ganglion calcifications, neuromotor impairments, epilepsy, stroke, and recurrent fever. Family history and consanguineous marriage are also common. IFN signature is a useful diagnostic tool and is positive in almost all patients with type 1 interferonopathies. Although IFN signature is a sensitive test, its specificity is relatively low. It can also be positive in viral infections and several connective tissue diseases. Therefore, next-generation sequence methods, whole exome sequencing (WES) in particular, are required for the ultimate diagnosis. The optimal treatment regime is still under debate due to a lack of clinical trials. Although high-dose steroids, anti-IL-1 and anti-IL-6 treatments, and reverse transcriptase inhibitors are used, JAK inhibitors are highly promising. Additionally, monoclonal antibodies against IFN-alpha and interferon-α receptor (IFNAR) are currently underway.

Type I interferonopathies are a novel group of disorders covered by Mendelian autoinflammatory diseases and are receiving attention in the last two decades. The diseases included in this group are characterized by varying degrees of autoimmunity and autoinflammation caused by an upregulation of type I interferons (IFNs) due to certain genetic alterations.[1]

Three types of IFNs that are highly potent polypeptides secreted by human cells have been described so far.[2] Type I IFNs, comprising predominantly IFN-α and IFN-β, are produced by nearly all nucleated cells. Their receptors are also ubiquitously expressed. They are mainly induced by viral infections and interfere with them by antiproliferative and modulator effects on mostly innate immune cells.[3] Type II IFNs or IFN-γ present their antiviral immune response via being activated by immune cells, mainly T-lymphocytes and natural killers.[4] Albeit type III IFNs or IFN-λ also have a substantial role in antiviral immunity, they are predominantly produced at the epithelial surface as the entry side of infection and are restricted in the related tissue distribution.[5]

Since IFNs have a key role in host immune defense, they have been tried in the treatment of several diseases and found to be beneficial in some, such as chronic hepatitis B/C, multiple sclerosis, and malign melanoma.[6] However, the idea that IFN overactivation may be harmful to mammals was suggested in 1980 for the first time. Gresser et al.[7] presented rodents with growth inhibition, delay in organ development, and liver and kidney injury due to IFN treatment. Hence, they emphasized that IFNs might be friend and foes alike for humans.

Advanced immunological assays showed that type I IFNs provide a tightly regulated major antiviral response, and they have paved the way for thoughts regarding the uncontrolled upregulation of type I IFNs as the underlying mechanism of several multisystemic diseases.[8] Rather than infection, systemic lupus erythematosus (SLE) is the first human disease found to be associated with enhanced levels of type I IFNs.[9] Then, a multisystemic disorder mainly characterized by neurological involvement resembling congenital viral infections called Aicardi-Goutières syndrome (AGS) was described as the first reported Mendelian type I interferonopathy.[10]

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Ongoing genetic and immunological assays performed in patients with similar clinical phenotypes led to the emergence of a new context called type 1 interferonopathies involving several distinct inherited inborn errors in 2011.[1] This review aimed to focus on these current, rare, and little-known groups of diseases.

PATHOGENESIS

Pathogen- and endogen-derived nucleic acids are sensed by pattern recognition receptors of mainly innate immune cells as danger signals, and type I IFNs are released to fight back. As we mentioned before, this downstream is tightly regulated. Any disruption in these sensitive regulation steps may cause enhanced type I IFNs, which are the key element of the pathogenesis of the diseases analyzed in this review.[11]

Cardinal pattern recognition receptors include toll-like receptors (TLRs), *retinoic acid-inducible gene-1* (*RIG-1*)-like receptors, *melanoma differentiation-associated* gene 5 (*MDA5*) receptors, and cyclic guanosine monophosphate-adenosine monophosphate (GMP-AMP) synthase (cGAS).[12-16] Moreover, TLRs such as TLR3, TLR7, TLR8, and TLR9 are present in macrophages, dendritic cells, and B lymphocytes, and TLR-depending nucleic acid sensing pathways ensue in these specialized immune cells. On the contrary, pathways related to other pattern recognition receptors such as cGAS, RIG-1, and MDA5 are ubiquitously expressed by various immune and non-immune cells.[17]

Deoxyribonucleic Acid (DNA) Sensing

After viral infections, the extracellular DNA and intracellular DNA of pathogens are degraded by deoxyribonuclease (DNase) 1 and DNase 2, respectively. If these enzymes are not functioning properly, non-self-DNA is increased in the cytosol.[18-20]

Nucleic acids in the nucleus called retroelements accounted for nearly half of the human genome. They are remnants of ancient viral infections and often do not replicate. However, these retroelements can sometimes undergo reverse transcription in the cytosol to produce cytosolic DNA (cDNA).[21] For the replication of self-DNA in the nucleus, the synthesis of initial ribonucleic acid (RNA)-DNA primer by DNA polymerase-α (encoded by *POL1A*) and the regulation of deoxynucleotide triphosphates by the SAM domain and HD domain-containing protein 1 (SAMHD1) are necessary. If the replication of self-DNA or its repair by removing ribonucleotides (RNASEH2A/2B/2C) is disrupted, it is damaged and leaks into the cytoplasm.[2,22-24]

A cytosolic DNase that lies on the nuclear membrane is called 3' repair exonuclease 1 (encoded by *TREX1*). If this enzyme losses its function, non-self-DNA, DNA sourced by retroelements, and damaged self-DNA are increased in the cytoplasm.[25] In addition, *LSM11* and *RNU7-1* gene mutations make histone stoichiometry disturbances in nuclear DNA and pave the way for sensing them by pattern recognition receptors.[26] The *ATAD3A* gene encodes a ubiquitously expressed mitochondrial membrane protein, and its mutation leads to mitochondrial partially processed DNA leakage into the cytoplasm.[27] These non-self and corrupted self-nucleic acids compose danger signals, and they are sensed by cGAS.[28]

Then, cyclic GMPAMP (cGAMP) is produced, and it activates the adapter molecule stimulator of interferon genes (STING) (encoded by *STING1* or *TMEM173*), which translocate the signal proteins from the endoplasmic reticulum (ER) to the Golgi apparatus (GA).[29,30] Coatomer subunit-α (COPA) is responsible for the retrograde vesicular transport of the proteins between the ER and GA. Therefore, negative mutations of the *COPA* gene result in abnormal STING trafficking.[30]

Ribonucleic Acid (RNA) Sensing

Conversely, while short RNA is sensed by RIG-1 (encoded by *DDX58*), long RNA is sensed by MDA-5 (encoded by *IFIH-1*).[2] Adenosine deaminase (encoded by *ADAR*) prevents double-strained RNA from being sensed by the deamination of adenosine to inosine.[31,32] An RNA helicase encoded by *SKIV2L* hinders cytosolic RNA from also being sensed.[30] When RIG-1 and MDA-5 sense cytosolic RNA, they activate mitochondrial antiviral signaling (MAVS) protein.[17]

Common Pathway in Nucleic Acid Sensing

STING by DNA or stimulating MAVS by RNA activates TANK-binding kinase 1 (TBK1) and an inhibitor of the nuclear factor κB kinase (IKK) complex. The activation of TBK1 and IKK results in the activation of transcription factors IFN regulatory factor 3 (IRF3) and nuclear factor-κB (NF-κB), respectively.[33]

Proteasomes in this context

Proteasome is an evolutionarily conserved organelle that plays a crucial role in protein degradation, and gene mutations related to its stabilization (*PSMA3, PSMB7, PSMB8, PSMB9, POMP, and PSMG2)* were found to be associated with uncontrolled type I IFN response.[2] Although the underlying mechanism has not been fully understood, recent insights present that these gene mutations cause the failure of proteasome complex formation. Then, misfolded proteins accumulate in the ER, and ER membrane proteins, particularly inositol requiring enzyme-1 (IRE1), are stimulated. Subsequently, IRE1 activates IRF3 and NF-κB.[34,35]

Nuclear Response

Then, IRF3 and NF-κB translocate to the nucleus. While IRF3 induces the transcription of IFN-β and IRF7, which is responsible for IFN-α releasing, NF-κB induces the release of proinflammatory cytokines, such as interleukin (IL-1), IL-6, and tumor necrose factor-α (TNF-α), which have inhibitory effects on IFN-α induction.[12,36] Ubiquitin-specific protease 18 (USP18), stabilized by *interferon-stimulated gene* (*ISG*) *15*, has a significant negative regulatory effect on ISG transcription. *ISG15* also optimizes the antibacterial response against mycobacterium.[37] However, osteopontin (OPN) is a cytokine that promotes type I IFN production. Tartrate-resistant acid phosphatase (encoded by *ACP5*) inactivates this function of OPN by dephosphorylation.[38] Although the mechanism remains unclear, early complement proteins such as C1q also hinder ISG transcription. This may be attributed to impaired processing and removal of immune complexes, culminating in the activation of autoreactive B-cells

and consequently reduced tolerance, concomitant with the inability to regulate IFN-α generation by plasmacytoid dendritic cells.[36]

Type I IFN Activity

Type I IFNs exert their effects in an autocrine and paracrine manner by binding to the interferon-α receptor (IFNAR), a cell surface receptor with two subunits, IFNAR1 and IFNAR2. The canonical type I IFN signaling pathway involves the activation of the Janus kinase (JAK)-signal transducer and activator of transcription pathway, leading to the transcription of target genes, including numerous IFN-stimulated genes. The binding of type I IFN to IFNAR1 and IFNAR2 triggers the activation of TYK2 and JAK1, which are members of the Janus family of tyrosine kinases.[39,40] Subsequently, activated TYK2 and JAK1 phosphorylate STAT1 and STAT2, respectively, forming the DNA-binding STAT1-STAT2-IRF9 ternary complex known as IFN-stimulated gene factor 3 (*ISGF3*). *ISGF3* then activates the transcription of genes that harbor an IFN-stimulated response element in their promoters.[30] Type I IFNs promote apoptosis of infected cells and alert surrounding non-infected cells mainly by maturation and proliferation of lymphocytes.[12,33] We tried to summarize the overall process of the type I IFN response in Figure 1.

Alterations that Cause Diseases

Gene mutations leading to the loss of function (LOF) of the negative regulators or gain of function (GOF) mutations of the positive regulators of this downstream cause type 1 interferonopathies by uncontrolled increased type 1 IFN response. The following mechanisms were previously proposed to cause type 1 interferonopathies: (1) excessive endogenous nucleic acid ligand accumulation, (2) alterations in endogenous nucleic acid ligand composition, (3) increased sensitivity or constitutive activation of a nucleic or non-nucleic acid receptor component of the type I IFN pathway, (4) disrupted negative regulation of the downstream, and (5) mutations in other genes that comprise adaptive immune response regulators.[41]

CLINICAL FEATURES

Although several diseases under the "type I interferonopathies" are caused by distinct genetic alterations, they share considerable amounts of mutual clinical findings that reflect their common pathogenic pathway disturbances.[42] They often develop in infancy, rarely were disease signs reported, even in the prenatal stage.[8] These inborn errors are characterized by autoinflammation and varying degrees of autoimmunity and immunodeficiency, and the skin, brain, and lungs are the organs most commonly involved.[2]

Unfortunately, only a few cohort studies have been published. Most of our knowledge is sourced from case reports. We tried to list the general characteristics of these diseases (Table 1) by compiling the current cohorts including at least five patients whose full texts are available.[29,43-46] Then, we summarized the overall genetic and clinical features of the diseases (Table 2). In addition, we presented some of the clinical and screening findings of our patients with their permission (Figure 2).

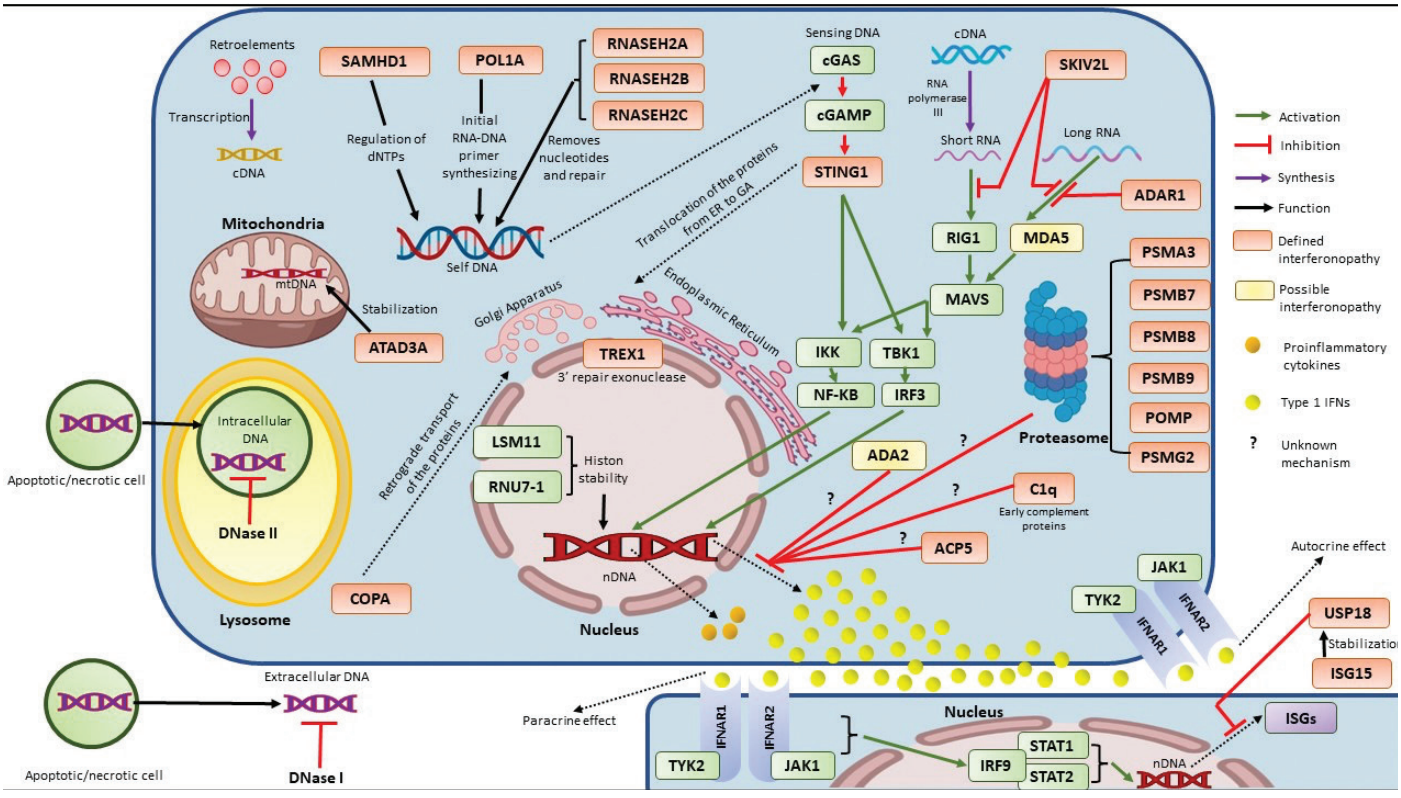

FIG. 1. A pathogenetic summary of the type I interferon response.

TABLE 1. Brief Description of Patients with Type 1 Interferonopathies.

Authors	Liu et al.	Wang et al.	Elhossini et al.	Yin Liu et al.	Batu et al.
Disease	SAVI	AGS	SPENCD	PRAAS	FSLE
Case number	6	23	5	9	7
Sex (F/M)	3/3	12/11	2/3	4/5	4/3
Age at disease onset	First 8 weeks of life 6/6	6 months (median)	14 months (mean)	First 6 months of life 9/9	32 months (mean)
Familial/sporadic	0/6	6/17	2/3	2/7	7/0
Fever	6/6	7/23	1/5	9/9	NA
Low weight and/or height	NA	11/21	5/5	9/9	NA
Skin involvement	6/6	11/23	2/5	9/9	7/7
Lipodystrophy	NA	NA	0/5	9/9	NA
Oral ulcers	NA	NA	NA	NA	5/7
Photosensitivity	NA	NA	NA	NA	6/7
Arthritis/arthralgia	1/6	3/23	5/5	9/9	4/7
Muscle atrophy	2/6	NA	0/5	4/9	NA
Intracranial calcification	NA	21/21	4/4	2/6	NA
Cognitive delay	NA	12/21	3/5	NA	NA
Motor deficits	NA	14/23	4/5	NA	NA
Hepatosplenomegaly	NA	2/21 (SM)	NA	7/9 (HM) and 3/9 (SM)	NA
Anemia	NA	1/23	3/3	9/9	4/7
Leukopenia	NA	2/23	2/5	1/9	3/7
Thrombocytopenia	NA	1/23	1/5	1/9	2/7
Hypocomplementemia	NA	4/11	NA	NA	3/7
ILD	5/6	4/21	NA	2/9	NA
Elevated liver enzymes	NA	8/19	NA	8/9	NA
Elevated APR levels	6/6	7/13	NA	9/9	NA
ANA positivity	3/6	6/12	NA	1/9	6/7
APLA positivity	5/6	NA	NA	NA	5/7
ANCA positivity	1/6	2/10	NA	2/9	NA

AGS, Aicardi-Goutières syndrome; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; APLA, anti-phospholipid antibody; APR, acute-phase reactant; F, female; FSLE, familial systemic lupus erythematosus; HM, hepatomegaly; ILD, interstitial lung disease; M, male; NA, non-available; PRAAS, proteasome-associated autoinflammatory syndromes; SAVI, STING-associated vasculopathy with onset in infancy; SM, splenomegaly; SPENCD, spondyloenchondrodysplasia.

Aicardi-Goutières Syndrome (AGS)

This is a highly heterogeneous group of diseases. Currently, mutations in seven different genes were found to be associated with AGS: *SAMHD1*, *ADAR1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *TREX1*, and *IFIH1*.[47]

The neonatal form presents with hepatosplenomegaly, thrombocytopenia, and microcephaly resembling congenital viral infections.[48] The early infantile form is characterized by slow or non-progressive neurological impairment after an abrupt encephalopathy phase, including dystonia, epilepsy, and motor-mental retardation.[43] The late-onset form presents a real diagnostic challenge because of its milder phenotype.[49]

Neuroimaging is a very useful diagnostic tool for AGS. Intracranial calcifications, parenchymal atrophy, and leukodystrophy are the most common findings.[50] Gene-specific neuroimaging findings such as *ADAR1*-related bilateral striatal necrosis and *SAMHD1*-related intracranial vasculopathy have been reported.[51,52] Lymphocytes and IFN-α are generally increased in patients' cerebrospinal fluid.[53]

Skin manifestations such as chilblain, livedo, nodules, and Raynaud's phenomena are also common. Other less frequently involved organs are the thyroid, lungs, kidneys, joints, and blood cells.[43]

TABLE 2. Summary of the Genetic and Clinical Features of Type I Interferonopathies.

	Gene	Inheritance	Clinical features
AGS	*SAMHD1, ADAR1, RNASEH2A, RNASEH2B, RNASEH2C, TREX1, and IFIH1*	AR/AD	Microcephaly, dystonia, epilepsy, motor-mental retardation, spasticity, CVD, ICC, chilblain, livedo, skin nodules, RP, cytopenia, and HSM
COPA	*COPA*	AD	ILD, DAH, arthritis, and renal disease
DADA2	*ADA2/CECR1*	AR	Livedo reticularis, hemorrhagic strokes, organ ischemia, and ID
FCL	*TREX1, SAMHD1*	AD	Early-onset, cold-induced chilblains in acral sites, arthralgia, and lymphopenia
FSLE	*TREX1, SAMHD1, ACP5, DNASE1, DNASE1L3, PRKCD, C1Q/R/S, C2, C3, C4*	AR/AD	Early-onset and refractory SLE, arthritis, lupus nephritis, malar rash, chilblain lesions, retinal vasculopathy, ICC, leukodystrophy, vision loss, stroke, and mental retardation
ISG15	*ISG15*	AR	ICC, epilepsy, dystonia, and increased mycobacterial infections
PRAAS	*PSMA3, PSMB7, PSMB8, PSMB9, POMP, and PSMG2*	AR	Recurrent fever, rash, growth retardation, HSM, muscle atrophy, lipodystrophy, and myositis
SAVI	*TMEM173/STING1*	AD	Recurrent fever, chilblain, livedo, telangiectasia, ILD, PHT, seropositive pJIA, short stature, renal disease, and ICC
SMS	*IFIH1, DDX58*	AD	Dental and skeletal abnormalities, aortal calcification, and glaucoma
SPENCD	*ACP5*	AR	Enchondromatosis-like metaphyseal lesions, platyspondyly, short stature, ICC, spasticity, intellectual disability, ID, and autoimmunity
THES	*SKIV2L, TTC37*	AR	Intractable diarrhea, liver abnormalities, facial dysmorphia, IUGR, growth failure, and ID
USP18	*USP18*	AD	ICC, microcephaly, ventriculomegaly, HSM, and thrombocytopenia
RVCL	*TREX1*	AD	Vision loss, neurocognitive impairment, CVD, migraine, RP, and renal disease
XLRPD	*POLA1*	AR	Reticulate hyperpigmented skin, ID, and fascial dysmorphia

AD, autosomal dominant; AGS, Aicardi-Goutières syndrome; AR, autosomal recessive; CVD, cerebrovascular disease; DADA2, adenosine deaminase 2 deficiency; DAH, diffuse alveolar hemorrhage; FCL, familial chilblain lupus; FSLE, familial systemic lupus erythematosus; HSM, hepatosplenomegaly; ICC, intracranial calcification; ID, immune deficiency; ILD, interstitial lung disease; ISG15, interferon-stimulated gene 15 deficiency; IUGR, intrauterine growth restriction; PHT, pulmonary hypertension; pJIA, polyarticular juvenile idiopathic arthritis; PRAAS, proteasome-associated autoinflammatory syndrome; SAVI, STING-associated vasculopathy with onset in infancy; SLE, systemic lupus erythematosus; SMS, singleton–Merten syndrome; SPENCD, spondyloenchondrodysplasia; THES, trichohepatoenteric syndrome; USP18, ubiquitin-specific protease 18 deficiency; RP, Raynaud's phenomena; RVCL, retinal vasculopathy with cerebral leukodystrophy; XLRPD, X-linked reticulate pigmentary disorder.

STING-Associated Vasculopathy with Onset in Infancy (SAVI)

SAVI is an autosomal dominant (AD) disorder with *TMEM173* (*STING1*) (encodes STING protein) gene mutation.[29] Recently, autosomal recessive (AR) cases were reported.[54] Fever episodes, skin manifestations that may cause acral tissue loss (e.g., digital amputation and nasal septum perforation) such as chilblain, livedo, and telangiectasia, and lung involvement, including interstitial lung disease (ILD) are the cardinal signs.[55]

Pulmonary hypertension, rheumatoid factor-positive polyarticular juvenile idiopathic arthritis, short stature, renal glomerular disease, myositis, mucosal involvement, alopecia, intracranial calcification, epilepsy, and spastic diplegia were also reported.[56]

COPA Syndrome

The COPA syndrome is an AD disease caused by the *COPA* gene mutation. Patients present with ILD that may result in pulmonary fibrosis, arthritis, and renal involvement, akin to SAVI. In contrast to SAVI, skin findings are absent, and diffuse alveolar hemorrhage can be seen.[55]

Familial Systemic Lupus Erythematosus (SLE)

Several gene mutations are responsible for this rare disease, including *TREX1, SAMHD1, ACP5, DNase1, DNase1L3*, protein kinase C δ (*PRKCD*), and genes encoding early complement proteins (C1q/r/s, C2, C3, and C4).[57] Although their clinical features are highly variable depending on genetic differences, they generally present in early childhood with atypical symptoms and poorly respond to conventional SLE treatment. In addition to arthritis, lupus nephritis, and dermatological signs such as malar rash and chilblain lesions that worsen with cold exposure, severe neurological findings including retinal vasculopathy, leukodystrophy, vision loss, stroke, and mental retardation can be observed.[58-62]

Familial Chilblain Lupus

Familial chilblain lupus is caused by a heterozygote mutation in *TREX1* or *SAMHD1*.[63,64] Early-onset and cold-induced bluish-red

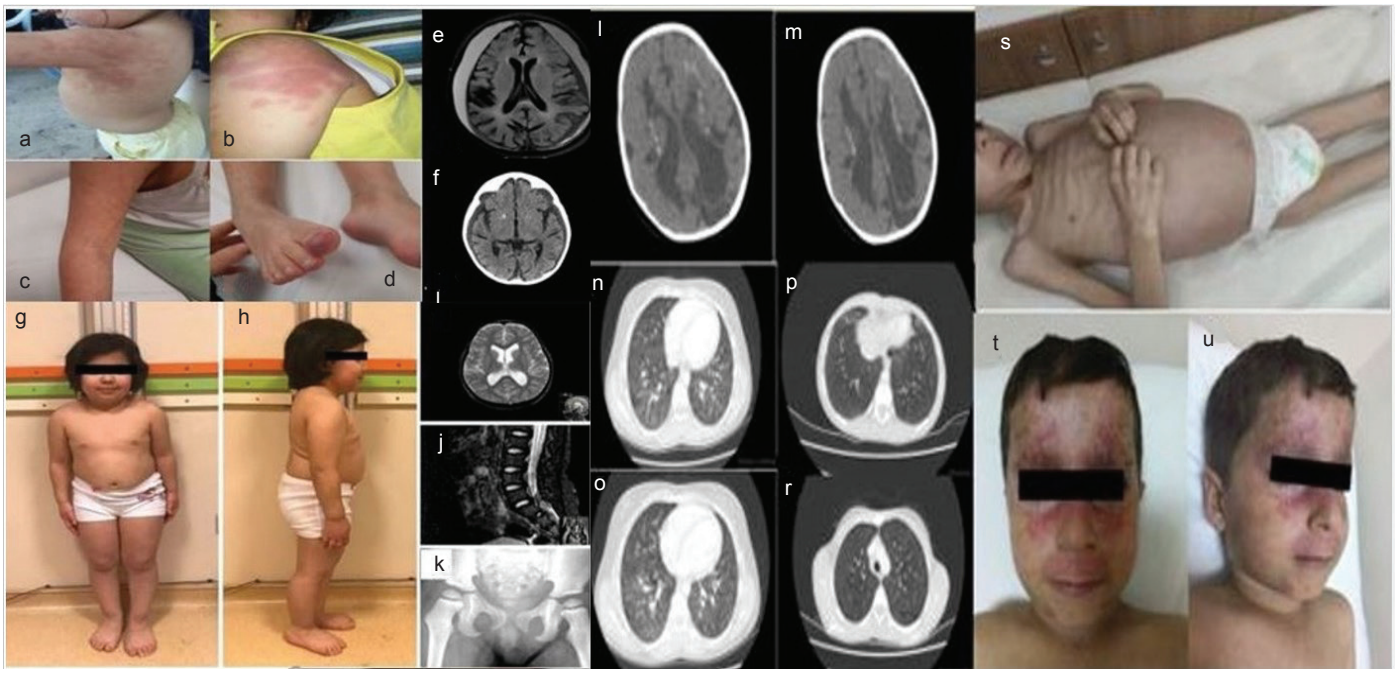

FIG. 2. Clinical and screening findings of our patients with type I interferonopathies. 8 years old girl with familial systemic lupus erythematosus (FSLE) (*homozygote C1Q* gene mutation): (a, b) Skin rash, (c) Livedoid rash, (d) Chilblain lesions on digital tips, (e) Subdural hematoma and cerebral atrophy, (f) Intracranial calcifications in magnetic resonance imaging (MRI). 4 years old girl with Spondyloenchondrodysplasia (*homozygote ACP5* gene mutation): (g, h) short stature, (i) mild ventricular dilatation and cortical atrophy in MRI, (j) platyspondyly of the lumbar vertebrae in MRI, (k) metaphyseal hyperintensity of proximal femur in X-ray. 3 years old girl with Aicardi Goutières Syndrome (*homozygote SAMHD1* gene mutation): (l, m) intracranial calcifications and ventricular dilatation in MRI. 11 years old girl with STING-associated vasculopathy with onset in infancy (*homozygote TMEM173* gene mutation): (n, o) bilateral ground glass opacity in chest computed tomography (CT). 4 years old girl with COPA syndrome (*homozygote COPA* gene mutation): (p, r) diffuse sub centimetric cyst and local honeycomb appearance accompanied by fibrotic changes in chest CT. 7 years old boy with Aicardi-Goutières Syndrome (*homozygote IFIH1* gene mutation): (s) abdominal distention and lipodystrophy. 4 years old boy with FSLE (Homozygote C1Q gene mutation): (t, u) malar rash.

lesions in acral sites, including fingers, toes, nose, cheeks, and ears, are the constant signs. In addition, arthralgia, lymphopenia, and anti-nuclear antibody positivity may be seen in some patients.[58]

Spondyloenchondrodysplasia (SPENCD)

SPENCD is inherited as AR and caused by *ACP5* mutation.[65] The cardinal sign of SPENCD is a severe skeletal dysplasia that results in short stature and is characterized by enchondromatosis-like metaphyseal lesions and platyspondyly. They may be accompanied by neurologic issues, including spasticity, intellectual disability, intracranial calcification, and immune deficiencies. They often develop an autoimmune disease such as SLE, Sjögren's syndrome, and autoimmune thrombocytopenia.[66]

Deficiency of Adenosine Deaminase 2 (DADA2)

Whether DADA2 is a type 1 interferonopathy is unclear.[55] However, ADA2, encoded by *ADA2* or *CECR1*, was shown to have a DNase activity, and its deficiency leads to cDNA accumulation, which induces STING-dependent type I IFN response.[67] Therefore, as reported by several authors before us, we strongly consider DADA2 as a member of type I interferonopathy.[11,68] The foremost manifestation of the disease involves vasculitis resembling early-onset polyarteritis nodosa, which can progress from livedo reticularis to potentially fatal ischemic or hemorrhagic stroke. Varying degrees of immunodeficiencies, lymphoproliferation, and cytopenia may also be seen.[69]

Trichohepatoenteric Syndrome (THES)

THES is caused by *SKIV2L* or *TTC37* mutations.[70] Infants with THES generally present with neonatal-onset intractable diarrhea and liver abnormalities.[71] They usually have typical facial dysmorphisms, including hypertelorism and woolly and patchy hair. Intrauterine growth restriction, failure to thrive, and immune deficiency are other common features.[70]

Singleton-Merten Syndrome (SMS)

SMS is an AD disease caused by a GOF mutation in the *IFIH1*.[72] Characteristic findings are dental abnormalities, periodontal diseases, skeletal defects, including osteolysis, and calcification in the aorta and heart valves.[42] An atypic form of the disease is caused by *DDX58* mutation. It is characterized by skeletal abnormalities, aortic calcification, and glaucoma.[73]

Interferon-Stimulated Gene 15 (ISIG15) Deficiency

ISG15 deficiency is inherited in an AR manner and is caused by *ISG15* mutations. Basal ganglion calcification and epilepsy are the typical features of this disease. Some of the patients may have autoantibody positivity. These patients are generally vulnerable to mycobacterial infections.[74]

Ubiquitin-Specific Protease 18 (USP18) Deficiency

USP18 deficiency is caused by a heterozygote LOF mutation in *USP18*. This disease is also called "pseudo-TORCH syndrome" because of similar symptoms such as microcephaly, ventriculomegaly, and intracranial calcifications in the absence of congenital infection. Some patients may have additional systemic symptoms, such as hepatomegaly and thrombocytopenia.[8]

Retinal Vasculopathy with Cerebral Leukodystrophy (RVCL)

RVCL is an AD disease caused by *TREX1* mutation. It generally onsets in early adulthood. Patients present with a loss of vision and neurocognitive impairment. Other manifestations include cerebrovascular diseases, migraine, Raynaud's phenomena, and renal symptoms.[75]

X-linked Reticulate Pigmentary Disorder (XLRPD)

XLRPD is caused by *POLA1* mutation. Boys and girls were not equally affected. Girls only have skin findings. However, boys present with, in addition to reticulate hyperpigmented skin, common infections (mainly respiratory and gastrointestinal infections), fascial dysmorphia, corneal dyskeratosis, and hypohidrosis.[11]

Proteasome-associated Autoinflammatory Syndromes (PRAAS)/Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE)

Mutations in *PSMA3, PSMB7, PSMB8, PSMB9, POMP, and PSMG2* are responsible for PRAAS or CANDLE. *This group of disorders is inherited in an AR manner and shares common findings such as fever attacks, increased levels of inflammatory markers, rash, growth retardation, hepatosplenomegaly, muscle atrophy, lipodystrophy, and myositis.*[2,42]

DIAGNOSIS

Because type 1 interferonopathies are extremely rare diseases, a strong clinical suspicion is the first step for an accurate diagnosis. Prepubertal-onset SLE with atypical symptoms, particularly severe neurological signs, and poor response to conventional treatment is highly suggestive. Furthermore, several features are common in most of the diseases in this group, such as vasculitic skin changes (including chilblains), panniculitis, ILD, basal ganglion calcifications, neuromotor impairments, epilepsy, stroke, recurrent fever, and autoimmunity. Given that these are Mendelian disorders, family history and consanguineous marriage are also noteworthy.[36,75]

The next step is the demonstration of an enhanced type 1 IFN response. However, their very low levels in the peripheral blood do not allow for appropriate measurements. Therefore, another method, i.e., the IFN signature, was developed, which depends on showing the expression of ISGs (IFIT1, IFI27, IFI44L, ISG15, RSAD2, and SIGLEC1) in the peripheral blood by polymerase

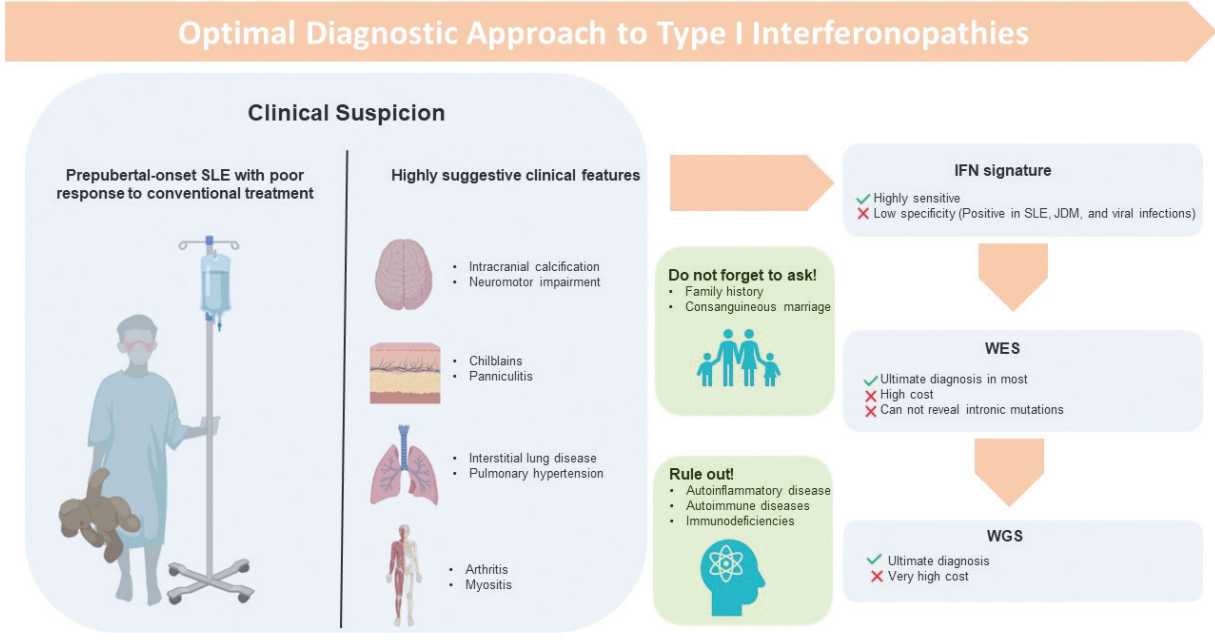

FIG. 3. Optimal diagnostic approach to type 1 interferonopathies. IFN: Interferon, JDM: Juvenile dermatomyositis.

SLE, systemic lupus erythematosus; WES, whole exome sequencing; WGS, whole genome sequencing.

chain reaction tests.[2] Given the difficulty in standardizing IFN signature tests between centers, a Nanostring assay-based ISG-28 scoring system is recently used.[76] The IFN signature is positive in nearly all patients with type 1 interferonopathies. However, few exceptions are noted. For instance, it is generally negative in patients with AGS having *RNASEH2B* mutation, even in the active disease phase.[55] Although the IFN signature is a sensitive test, its specificity is relatively low. It can also be positive in viral infections, SLE, juvenile dermatomyositis, and type II/III IFN increment.[41,77,78]

Considering the limitations of the IFN signature, a clinical scoring system was proposed, particularly for distinguishing type I interferonopathies from certain rheumatic diseases.[78] Given the genetic background of this group of disorders, next-generation sequencing methods, particularly whole-exome sequencing, are required for the ultimate diagnosis.[77] However, since the mutations in XLRPD are intronic, whole-genome sequencing should be performed.[76] The optimal diagnostic approach to this rare and novel group of diseases is presented in Figure 3.

TREATMENT

The optimal treatment regimen is still under debate due to the lack of clinical trials. High-dose steroids, anti-IL-1, and anti-IL-6 treatments were shown to be partially effective. Monoclonal antibodies against IFN-α (sifalimumab) and IFNAR (anifrolumab) are currently under phase 2 and 3 trials. JAK inhibitors such as tofacitinib (inhibits JAK1 and JAK3), ruxolitinib (inhibits JAK1 and JAK2), and baricitinib (inhibits JAK1) are highly promising. However, they are not sufficient to recover lung involvement.[76] The most common adverse events of JAK inhibitors are BK viremia and respiratory and gastrointestinal infections.[79] In addition, reverse-transcriptase inhibitors such as abacavir, lamivudine, and zidovudine were used and shown to provide a transient improvement.[80]

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