Hematopoietic stem cell transplantation in combined immunodeficiency with associated or syndromic features

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به نام خداوند جان و خرد
کز این برتر اندیشه بر نگذرد

خداوند نام و خداوند جای
خداوند روزی ده رهنمای

خداوند کیوان و گردان سپهر
فروزنده ماه و ناهید و مهر

ز نام و نشان و گمان برتر است
نگارنده بر شده پیکر است

ابوالقاسم فردوسی

Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification

IIa. CID with associated or syndromic features

Congenital thrombocytopenia

XL: **Wiskott Aldrich Sd or XL thrombocytopenia *WAS (LOF)*.** Recurrent bacterial and viral infections; bloody diarrhea; eczema; lymphoma; autoimmune disease; IgA nephropathy; vasculitis. Small platelets; Decreased IgM. Low antibody to polysaccharides; often increased IgA and IgE. Nl Bc. Tc: Progressive decrease in numbers; Low Tc responses to anti-CD3.
Patients with XL-thrombocytopenia have later onset of complications and more favourable life expectancy but eventually develop similar complications as observed in WAS

AR: **WIP deficiency*. *WIPF1,*** WAS protein absent. +/- small platelets; increased IgE. Bc : Nl to low. Tc: Reduced; defective lymphocyte responses to anti-CD3.

AR: **Defective Arp2/3-mediated filament branching. *ARPC1B.*** Recurrent invasive infections, colitis, vasculitis. Mild trombocytopenia, normal sized platelets; autoantibodies (ANA, ANCA); eosinophilia.High IgA and IgE.

DNA Repair Defects other than those listed in Table1: Karyotype

Ataxia telangiectasia. *ATM:* Ataxia; telangiectasia; pulmonary infections; lymphoreticular and other malignancies; increased α-fetoprotein; increased radiosensitivity, chromosomal instability and translocations. Often decreased IgA, IgE and IgG subclasses; increased IgM; antibodies variably decreased. Tc : Progressive decrease, abnormal prolif to Mitogens.

Nijmegen breakage Sd. *NBS1.* Microcephaly; bird-like face; lymphomas; solid tumors; increased radiosensitivity; chromosomal instability. Often decreased IgA, IgE and IgG subclasses;increased IgM; antibodies variably decreased. Bc: Variably reduced. Tc: progressive decrease.

Bloom sd. *BLM.* Short stature; bird like face; sun-sensitive erythema; marrow failure; leukemia; lymphoma; chromosomal instability. Low Ig.

PMS2 def. *PMS2.* Café-au-lait spots ; lymphoma, colorectal carcinoma, brain tumors. HIGM and abnormal antibody responses. Reduced Bc, switched and non-switched.

Immunodeficiency with centromeric instabiltiy and facial anomalies: ICF1. *DNMT3B;* ICF2:*ZBTB24;* ICF3:*CDCA7;* ICF4:*HELLS.* Facial dysmorphism; macroglossia; bacterial/opportunistic infections; malabsorption; malignancies. Cytopenias; multiradial configurations of chromosomes 1,9,16; no DNA breaks. Ig: Hypogammaglobulinemia; Tc and Bc: decreased or Nl.

MCM4 def. *MCM4.* Viral infections:EBV,HSV,VZV.short stature.Bc lymphoma; Adrenal failure; NKc low number and function.

RNF168 def* (RIDDLE sd). *RNF168.* Short stature; mild defect of motor control to ataxia; normal intelligence to learning difficulties; mild facial dysmorphism to microcephaly; increased radiosensitivity. Low IgG or IgA.

POLE1 (Polymerase ε subunit 1) deficiency (FILS syndrome). *POLE1.* Recurrent respiratory infections; meningitis; facial dysmorphism, livido, short stature. Low IgM, lack of antibody to PPS. Low memory Bc. Decreased Tc proliferation.

POLE2 (Polymerase ε subunit 2) deficiency. *POLE2.*** Recurrent infection, disseminated BCG infections, autoimmunity (type 1 diabetes, hypothyroidism), facial dysmorphism; Low Ig; Very low Bc. Lymphopenia, lack of TRECS, absent proliferation of antigens.

NSMCE3 deficiency*. *NSMCE3.* Severe lung disease (possibly viral); thymic hypoplasia, Chromosomal breakage; radiation sensitivity. Ig: Decreased Ab responses to PPS, normal IgG, IgA, normal to elevated IgM. Tc : Low, poor responses to mitogens and antigens.

Ligase I deficiency *. *LIGI* Recurrent bacterial and viral infections; growth retardation; sun sensitivity; lymphoma; radiation sensitivity. Macrocytic red blood cells. Hypogammaglobulinemia. Reduced Ab response. Lymphopenia, increased γδTc, decreased mitogen response.

GINS1 def*. *GINS1.* IUGR. Neutropenia, NK cells very low. Tc and Bc: low or normal. High IgA, Low IgG and IgM.

BMFS2 (Hebo def). *ERCC6L2,* AR. Facial dysmorphism; microcephaly, learning difficulties. Bone marrow failure.

Immuno-osseous dysplasias

Cartilage Hair Hypoplasia *RMRP.* Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure; autoimmunity; susceptibility to lymphoma and other cancers; impaired spermatogenesis; neuronal dysplasia of the intestine. Ig: Nl or ↓. Tc: Varies from ↓↓ (SCID) to Nl; impaired lymphocyte proliferation.

Schimke Sd *SMARCAL1* Short stature, spondilo-epiphyseal dysplasia, IUGR; nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure. Tc: ↓

MOPD1 Deficiency. *RNU4ATAC.* Recurrent bacterial infections, lymphadenopathy, Spondyloepiphyseal dysplasia, IUGR, retinal dystrophy, facial dysmorphism; +/- microcephaly. short stature. Ig: ↓ , specific antibodies variably decreased

Immunoskeletal dysplasia with neurodevelopmental abnormalities. *EXTL3.* Short stature; cervical spinal stenosis, neurodevelopmental impairment. Eosinophilia; Ig: variably ↓ Tc: ↓

MYSM1 def* *MYSM1,* AR Short stature, congenital bone marrow failure, myelodysplasia. Skeletal anomalies; cataracts; developmental delay. Affects granulocytes. Bc: immature. Tc: lymphopenia, reduced naïve Tc. Hypogammaglobulinemia

Thymic Defects with Additional Congenital Anomalies

AD. Hypoparathyroidism, conotruncal cardiac malformation, velopalatal insufficiency, facial dysmorphism, intellectual disability . Ig : Normal or decreased. Tc: ↓or Nl May have low TRECs at NBS.
DiGeorge/velocardiofacial Sd. Chr22q11.2 deletion Sd. 22q11.2DS.
TBX1 deficiency . *TBX1*

Chromosome 10p13-p14 deletion Syndrome. *10p13-p14DS.* AD. Hypoparathyroidism; renal disease; deafness; growth retardation; facial dysmorphism; cardiac defects may be present

AD. CHARGE Sd. *CHD7, SEMA3E.* Coloboma, heart anomaly, choanal atresia, intellectual disability, genital and ear anomalies; CNS malformation; some are SCID-like and have low TRECs. Ig: Normal or decreased. Tc: Decreased or normal; response to PHA may be decreased

Jacobsen Sd. *11q23del.* Recurrent respiratory infections; multiple warts; facial dysmorphism, growth retardation. Lymphopenia, Low NK, Bc and switched memory Bc. Hypogammaglobulinemia.

FOXN1 haploinsufficiency. *FOXN1,* AD
Recurrent, viral and bacterial respiratory tract infections; skin involvement (eczema, dermatitis), nail dystrophy. T cell lymphopenia may normalize by adulthood.

Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification

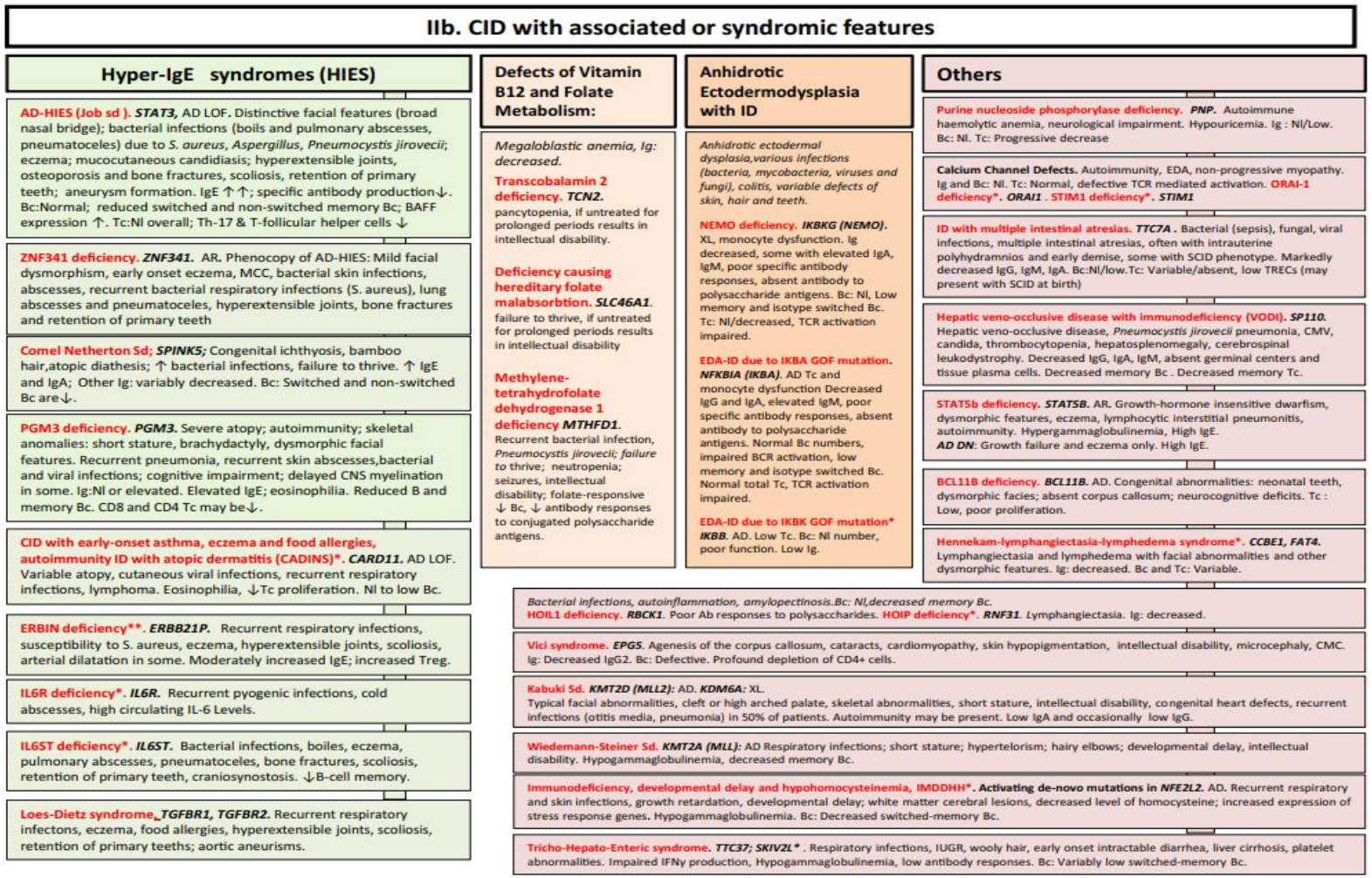
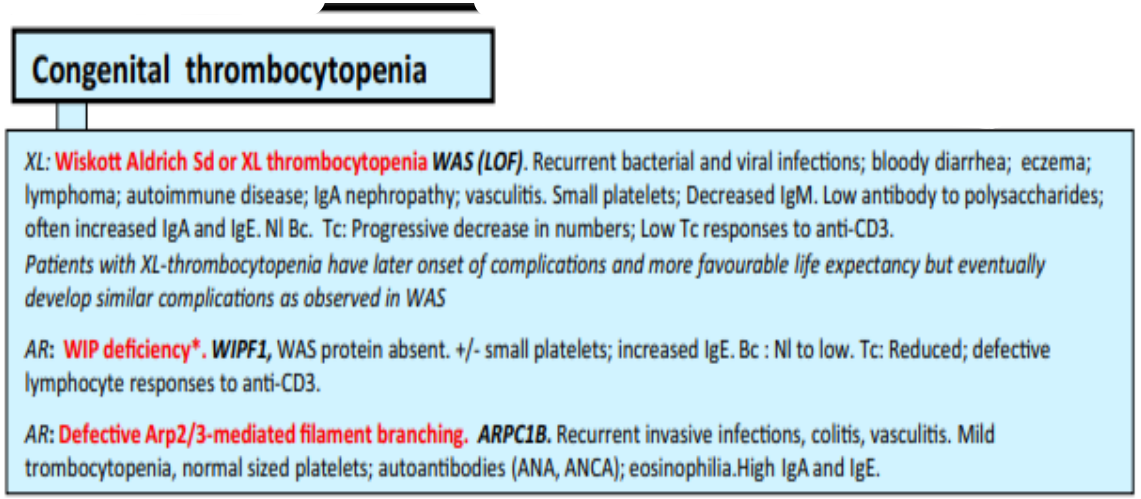


Fig. 2 (continued)



Wiskott-Aldrich syndrome (WAS):

- an X-linked disorder /Mutations of the *WASP* gene
- characterized by microplatelet thrombocytopenia, eczema, recurrent infections, and an increased risk of autoimmunity disorders and lymphoreticular neoplasia.
- Mutations of the *WASP* gene :

1. WAS
2. chronic or intermittent X-linked thrombocytopenia
3. (XLT)X-linked neutropenia (XLN)

- XLT is a milder form of WAS characterized by micro thrombocytopenia.
- XLN is characterized by congenital neutropenia and an increased risk of myelodysplasia.
- The classic clinical triad of WAS: bleeding, infection, eczema
- These symptoms are usually not present simultaneously. The earliest manifestations, often present at birth, are petechiae and bruises.
- Life-threatening hemorrhage (in 30% of WAS/XLT patients)
- Recurrent severe bacterial, viral, or fungal infections (may be difficult to treat and become life-threatening)
- Otitis media, sinusitis, meningitis, sepsis, diarrhea, and pneumonia are caused by common organisms

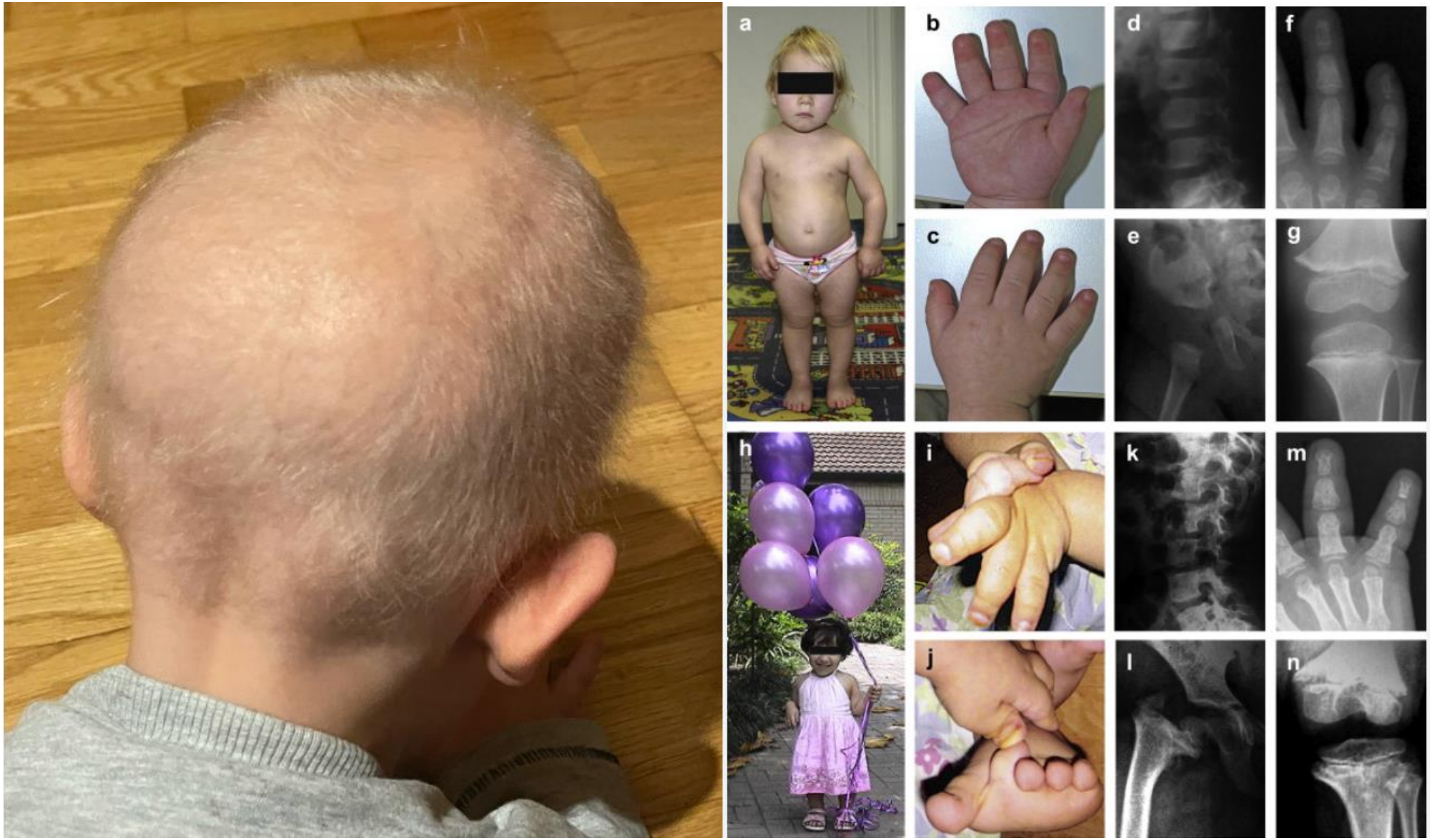
- Eczema: ranging from mild and localized to severe and generalized/ usually develops during the first year of life
- Other manifestations: pallor, failure to thrive, generalized lymphadenopathy, hepatosplenomegaly, arthritis, vasculitis, and keratitis
- Autoimmune diseases: happens in 22-72% pts

- Diagnosis of WAS:
- Male with congenital or early-onset (or even transient) thrombocytopenia and small platelets, especially if other male relatives have been affected.
- A history of mild or severe eczema
- Infections and immunologic abnormalities
- Autoimmune diseases and/or malignancies
- Flow cytometric analysis of lymphocytes for decreased or absent levels of intracellular WASP is a screening method
- The gold standard test: identify a mutation of the *WASP* gene by sequence analysis

- prophylactic IVIG for patients with significant antibody deficiency
- Prophylaxis with trimethoprim sulfamethoxazole (to prevent PJP), and acyclovir
- irradiated and negative for cytomegalovirus platelet transfusions in serious bleeding such as central nervous system hemorrhages, surgery
- Aspirin is contraindicated.
- Eltrombopag (Thrombopoietin receptor agonist) for ITP
- For some XLT patients with severe bleeding, splenectomy is life-saving by increasing the number of circulating platelets.
  - However, splenectomy significantly increases the risk of septicemia in XLT and death in the WAS following subsequent HSCT.
- The only curative therapy for WAS is HSCT and gene therapy.

- **WIP deficiency:**
- Autosome recessive, mutation in *WIPF1* gene
- Clinical presentation is the same as WAS
- thrombocytopenia with normal platelet volume
- low number of T and B cells, increased NK cells
- normal IgG and mildly increased IgE levels
- completely defective T cell proliferation to antiCD3
- abnormal NK cell function
- Diagnosis of WIP deficiency should be considered in any patient with WAS features who demonstrates undetectable *WASP mutation.*

- **Cartilage-hair Hypoplasia:**
- autosomal recessive/ mutations in *RMRP* gene
- predominantly T cell deficiency associated with metaphyseal chondrodysplasia(a form of short-limbed dwarfism)
- The hallmark features are: short stature, cell-mediated immune deficiency, bone marrow dysplasia, Hirschsprung's disease, and predisposition to malignancy, Birth weight is generally normal, dwarfism is usually apparent at birth because of short extremities, normal head circumference, short and pudgy hands with short fingernails, loose joints, silky white or yellow color, very sparse and fine hair of scalp, eyebrows, and eyelashes that tends to darken with age.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- Increased susceptibility to infection in 33-50%
- Mild anemia is frequent in early childhood, improving with age
- Severe hypoplastic anemia in 6%
- Neutropenia (usually consequent to failed marrow production but also sometimes autoimmune) is frequent.
- Autoimmunity due to immune dysregulation
- The immune deficiency is variable.
  - T cell lymphopenia, and reduced delayed type hypersensitivity
  - Diminished proliferative responses to concanavalin A, phytohemagglutinin, and pokeweed mitogen

- IgG and IgA levels may be reduced.
- Antibody responses to protein antigens are usually normal but may be suboptimal to some polysaccharide vaccine antigens.

- Management:
- Immunoglobulin therapy in significant antibody defect
- In profound T cell defects, start infection prophylaxis and candidate the patient for hematopoietic stem cell transplantation (HSCT)

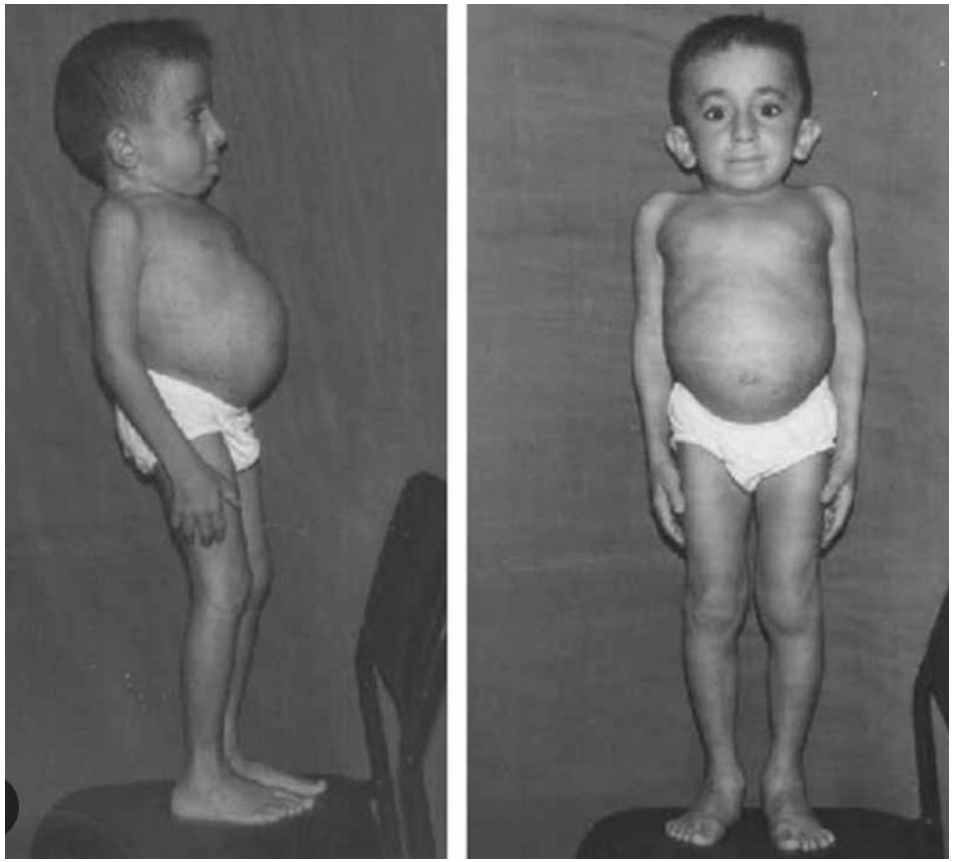
- **SCHIMKE'S IMMUNO-OSSEOUS DYSPLASIA:**
- Autosomal recessive/ mutation in *SMARCAL1* gene
- Characterized by: spondyloepiphyseal dysplasia causing short stature, facial dysmorphism, steroid-resistant nephrotic syndrome leading to progressive loss in kidney function and defective cellular immunity
- Opportunistic infections due to T cell immune deficiency
- Bone marrow failure is seen in about 10%
- Growth failure is usually the first feature. (IUGR in more than 2/3rd of patients and postnatal growth retardation invariably occurs)
  - Growth failure affects trunk length. A sitting height to leg length ratio of less than 0.83 is suggestive of SIOD

Box 6.7 Hallmark Features of SIOD

- Short stature with SED, short trunk and neck
- Steroid-resistant nephrotic syndrome
- Hyperpigmented macules
- Lymphopenia (T cell)
- Intermittent cerebrovascular insufficiency (50%)
- Bone marrow failure (10%)

Other Features

- Microdontia; corneal opacities
- Fine coarse hair
- Osteopenia
- Elevated TSH, euthyroid
- Normal intellectual development
- Bone marrow hypoplasia



- The diagnosis is suspected in a child with nephrotic proteinuria and disproportionate growth failure.

- Immunologic findings:
- T cell lymphopenia
- Normal B cell count
- Impaired delayed hypersensitivity and lymphocyte proliferative responses
- Anemia, neutropenia, and thrombocytopenia (30-60%)

- Management:
- eventually require renal replacement therapy
  - Reduced intensity immunosuppression after renal transplantation can result in a good graft outcome with a reduced number of severe infections.
- Erythropoietin-resistance anemia
- G-CSF may indicate for neutropenia
- Successful bone marrow transplantation has been reported in SIOD, correcting marrow failure and the immune deficiency.

- DNA Repair Defects:

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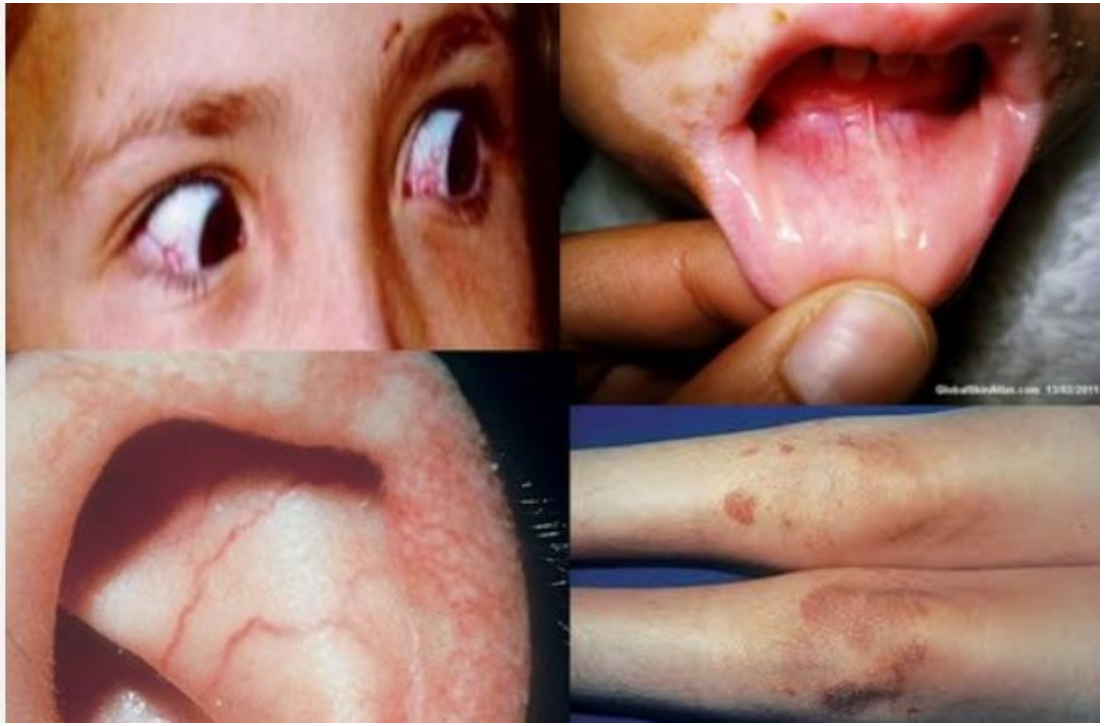
- **Ataxia telangiectasia:**
- autosomal recessive disease/ mutations of the *ATM* gene
- progressive neurodegeneration, immune deficiency, telangiectasias, high cancer risk, and premature aging
- A-T is often referred to as a genome instability or DNA damage response syndrome.
- first reported in 1926
- Clinical presentation: cerebellar ataxia, telangiectasia, ocular apraxia, dysarthria, drooling, choreoathetosis, clubbing, hypogonadism, skin granuloma, progeric changes (hair, skin), recurrent infection, chronic lung disease, increased risk of diabetes, increased risk of cancer, chromosomal instability, radiosensitivity, elevated AFP

- The lifetime prevalence of cancer is estimated to occur in 10%- 30% of A-T patients, and the incidence is 60- 184 times greater than in an age-matched population.
- In a French cohort of 279 patients with A-T, 69 patients with cancer (24.5%) were reported, mainly non-Hodgkin lymphomas (28 cases).
- Overall survival was shorter in the A-T group with cancer
- Hypogammaglobulinemia occurred in 15.5% , hyper IgM due to defects in the class switch recombination in 45%.
- Defects in the production of antibodies against pneumococcal antigens.



- B cell lymphopenia was found in 59.5% and T cell lymphopenia in 61.9%.
- decreased total CD4+Tcells and CD4/CD45RA cells
- a small thymus with embryonic morphology and absent Hassall's corpuscles
- should be suspected when a child presents with cerebellar ataxia and ocular telangiectasia and lymphocytopenia in newborns
- confirmed by an elevated serum level of a-fetoprotein (AFP) (>10 ng/mL). (test is most reliable after 2 years of age)
- The lack of ATM protein on Western blotting, proof of radiosensitivity, and the demonstration of a mutation on the *ATM* gene may contribute to the diagnosis.

- Based on the European Society for Immune Deficiencies (ESID)
- A definitive AT: either increased radiation-induced chromosomal breakage in cultured cells or progressive cerebellar ataxia, which has disabling mutations on both alleles of the *ATM* gene.
- A probable AT: progressive cerebellar ataxia and three out of the following four findings:

1. ocular or facial telangiectasia
2. serum immunoglobulin A at least 2 SD below normal for age
3. AFP at least 2 SD above normal for age
4. increased radiation-induced chromosomal breakage in cultured cells

- A possible AT: progressive cerebellar ataxia has at least one of the previous four findings.

- Immunoglobulin replacement, antioxidants, neuroprotective factors are commonly used for A-T treatment, but, to date, there is no known cure.
- Some case reports of A-T patients have shown that BMT is becoming a good option, as correct engraftment can restore some aspects of immunologic capacity.
    - Non-myeloablative conditioning is required before BMT.
- Although BMT might be considered one promising therapy for the treatment of immunological defects and cancer prevention in selected A-T patients, the therapy is currently not recommended or recognized and the eligibility of A-T patients for BMT is a point to deepen and deliberate.

cancers

MDPI

Review

Bone Marrow Transplantation as Therapy for Ataxia-Telangiectasia: A Systematic Review

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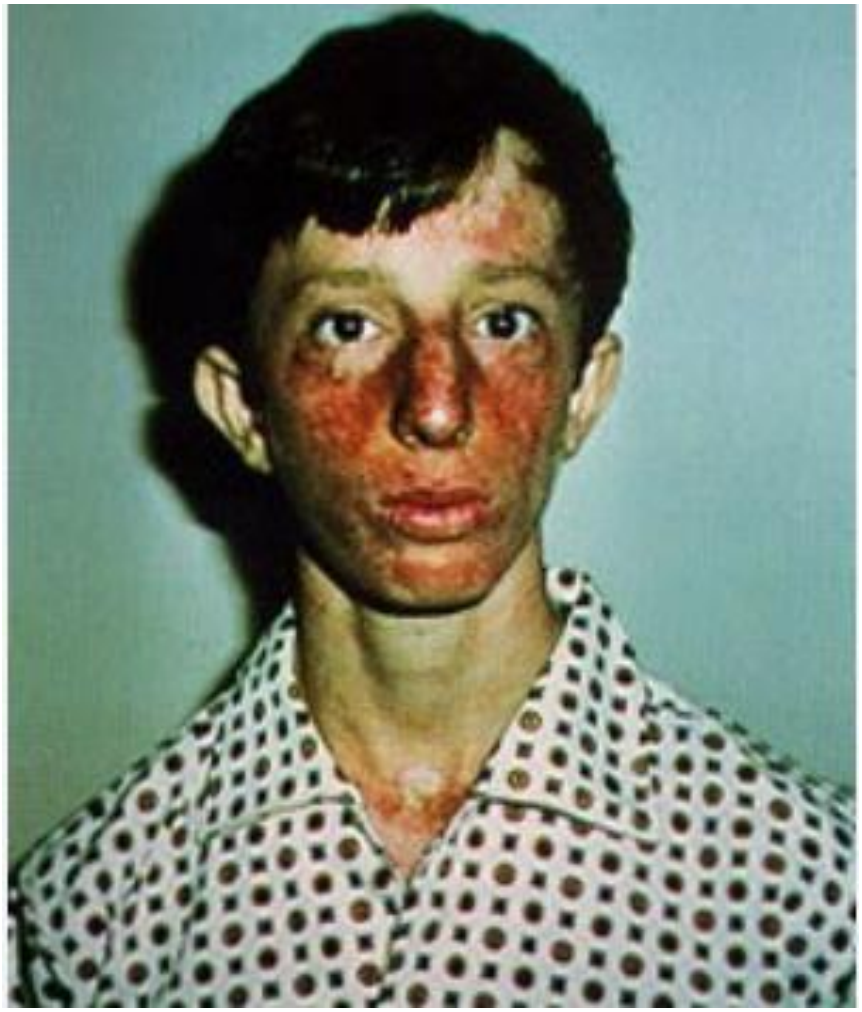
Simple Summary: Ataxia-Telangiectasia is a rare neurodegenerative disease and patients die in their early forties mainly because of immunodeficiency, leukemia and lymphoma. In this work we describe the different routes of diagnosis, the recent treatments, and the emerging therapies for the disease. Bone marrow transplantation from siblings or an unrelated donor is becoming an option of therapy for selected Ataxia-Telangiectasia patients to deal with the immunodeficiency and to prevent leukemia and lymphoma. The patients require a non-myeloablative conditioning before bone

- Mutation-targeted therapies:
- any attempt to restore normal function to mutant ATM through mutation-targeted therapy would require a read-through of the termination codon or concealment of the cryptic splice site. Any such approach does not necessarily have to restore normal levels of protein since even low levels of ATM (5%–10%) in some A-T patients result in a considerably milder phenotype.

- **Bloom syndrome**
- first described in 1954
- autosomal recessive disease/ mutations in the *BLM* Gene
- Manifests as:
- proportionate severe pre- and postnatal growth deficiency, sparseness of subcutaneous fat tissue, erythematous skin lesions of the face, feeding problems, recurrent infections, chronic lung disease/bronchiectasis, increased risk of diabetes, immune deficiency, increased risk of cancer, poor thought performance, and radiosensitivity

- Facial features include a small and narrow cranium with prominence of nose and ears
- Malar rash due to photosensitivity
- Short height with normal body proportions in all periods of life
- Chronic bronchitis and bronchiectasis is frequent, leading to chronic obstructive lung disease as cause of death.
- Type 1 diabetes mellitus has been seen in 17.7% of cases
- Myelodysplasia is reported in 8% of cases, some of them progressing to leukemia.
- The most common cause of death is malignancy, in different anatomic sites, presents at earlier ages and is more frequent than in other DNA repair diseases



The immune deficiency is variable and not severe.

- Low immunoglobulin levels
- Normal antibody responses to vaccines
- Normal lymphocyte subpopulations
- Normal absolute lymphocyte counts
- Normal T cell mitogen stimulations

Diagnosis is confirmed by:

- Sister chromatid exchange (SCE)
  - in which an average result of 40-100 per metaphase is not normal, compared to controls where the result is ,10 per metaphase.
- In a doubtful SCE test, perform a cytogenetic test in dermal fibroblasts.
- mutations in the *BLM* gene
- SCE analysis is also useful for prenatal diagnosis.

Assessment of the patient :

- growth parameters
- fasting blood glucose, serum immunoglobulins, and stool guaiac test
- cancer diagnosis must be established
- Avoidance of DNA-damaging chemicals and ionizing radiation
- The use of growth hormone has not proved to be effective.
- protection against sun exposure
- Replacement with IV or SC IG in the presence of hypogammaglobulinemia
- PEG may be indicated to recover nutrition

Nijmegen Breakage Syndrome:

- Autosomal recessive disease
- mutations in the gene *NBN*
- The protein is part of the MRN complex, thus, it has an important role in cellular response to DNA damage and in the maintenance of chromosomal integrity.
- Clinical presentation: microcephaly, mild growth delay, dysmorphic face, premature ovarian insufficiency, skin granulomas, recurrent infections, immune deficiency, increased risk of cancer, chromosomal instability, radiosensitivity

- Microcephaly is present at birth in 75% of cases and is progressive.
- The anterior fontanel is hardly palpable in new borne, and it closes during the first weeks of life.
- dysmorphic face, prominent midface, sloping forehead, large ears, and receding mandible, upwardly slanted palpebral fissures and a long, beaked and upturned nose with anteverted nostrils
- good psychomotor development
- speech delay and progressive deterioration of cognitive development
- Over 40% of patients develop a malignancy by the age of 20 years, mainly of lymphoid origin, Non-Hodgkin lymphomas(the most frequent)

- The immune deficiency is variable
- half of patients develop lymphopenia and leukopenia
- CD3+CD4+T Lymphopenia in 90% of cases
- CD4+ CD45RA+ T cells are decreased
- B cell lymphopenia in 72-75%
- Reduced T cell LTT to mitogens
- Negative delayed hypersensitivity skin test
- Hypogammaglobulinemia is found in 20-40% of patients, but 20% of cases have normal serum immunoglobulin levels.
- abnormal antibody responses to specific antigens and vaccines
- A persistent monoclonal gammopathy of IgM and/ or IgG isotypes has been reported.

- Immunoglobulin replacement is indicated in hypogammaglobulinemia or IgG2 deficiency in the setting of infections.
- manage developmental and speech delays, school problems, chronic lung disease, and cancer treatment.
- Hematopoietic stem cell transplantation has been reported as a successful treatment in NBS cases with lymphoma; it treated the lymphoma and restored T cell immunity.

- Cause of death: malignancy, chronic lung disease, and, in some cases, renal failure as a result of amyloidosis.

- **RIDDLE syndrome:**
- An autosome recessive disease
- mutations in the *RNF* gene that encodes the ring finger protein 168 (RNF168), an E3 ubiquitin ligase protein involved in DNA double-strand break (DSB) repair.
- leads to abnormal class-switch recombination (CSR)
- characterized by radiosensitivity, immune deficiency, facial dysmorphism, learning difficulties, and short stature, Deficient motor control (mild) stature, Low serum IgG

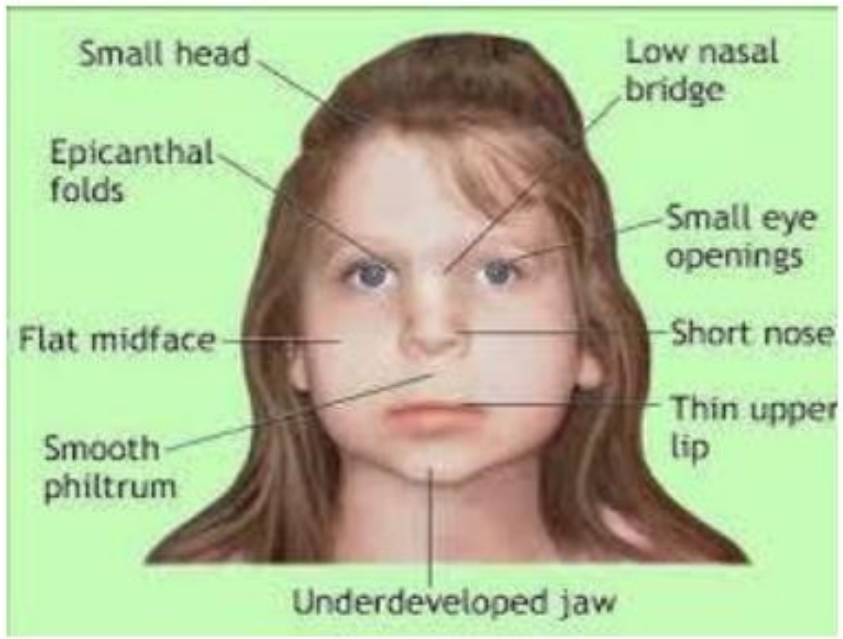
- IGRT for the hypogammaglobulinemia
- protection against radiation
- There are not enough data available to discuss the cancer risk in patients or their families.

- **Defects in Thymic Development: DiGeorge/CHARGE/Chromosome 22q11.2 Deletion**
- **DiGeorge anomaly:**
- variable in presentation, predispose to recurrent infection, autoimmunity and allergy
- The three main features of DiGeorge anomaly: congenital heart disease, hypocalcemia from hypoparathyroidism, low T cell counts (from a small thymus)
- at least two of these features are needed for the diagnosis
- Children with DiGeorge anomaly may have multiple other associated clinical symptoms

- DiGeorge anomaly can occur in 22q11.2 hemizygosity, CHARGE syndrome, and infants of diabetic mothers.
- partial DiGeorge anomaly have a small thymus or low T cell numbers.
- complete DiGeorge anomaly have no functioning thymus as determined by the lack of T cells (or the lack of thymically-derived naıve T cells).

TABLE 8.2 Genetic and Syndromic Associations with DiGeorge Anomaly

Diagnosis	Partial DiGeorge[a]	Complete DiGeorge[b]
22q11.2DS	55%	48%
CHARGE syndrome	2%	24%
Infant of diabetic mother	8%	16%
Other deletions/duplications	5%	
VATER	2%	
Ethanol or cocaine exposure	3%	
No association identified	27%	12%



- **Diagnosis of Partial DiGeorge Anomaly**
- Two of the following three conditions are required:

1. Congenital heart defect
2. Hypoparathyroidism
3. 3. Small thymus determined either by

a) A small or absent thymus at heart surgery

b) T cell counts or naive CD4 and naive CD8 counts less than the 10th percentile for age (a surrogate marker for a small thymus)

Note that the presence of 22q11.2DS or CHARGE syndrome is not sufficient to make the diagnosis of partial DiGeorge anomaly.

Criteria for the Diagnosis of Complete DiGeorge Anomaly

Athymia plus one of the following:

- Congenital heart disease
- Hypoparathyroidism
- 22q11.2DS
- CHARGE syndrome

- Athymia in the context of DiGeorge anomaly is defined as having fewer than 50 naive T cells/mm3 or less than 5% of total T cells being naive in phenotype.

- Treatment options include: bone marrow transplantation or thymus transplantation
- Without thymic or hematopoietic cell transplantation, these patients die by 12 months of age.
- Even with a transplant, however, prognosis remains poor. In a study of 50 infants who received a thymic transplant for complete DGS, only 36 survived to two years.

- Prognosis of pt with partial DiGeorge syndrome:
- depends on the severity of the pathologies associated with the disease, while some do not survive infancy due to severe cardiac anomalies, many survive into adulthood.

Thymus transplantation for complete DiGeorge syndrome: European experience

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Background: Thymus transplantation is a promising strategy for the treatment of athymic complete DiGeorge syndrome (cDGS).

Methods: Twelve patients with cDGS underwent transplantation with allogeneic cultured thymus.

Objective: We sought to confirm and extend the results previously obtained in a single center.

Results: Two patients died of pre-existing viral infections without having thymopoiesis, and 1 late death occurred from autoimmune thrombocytopenia. One infant had septic shock shortly after transplantation, resulting in graft loss and the need for a second transplant. Evidence of thymopoiesis developed from 5 to 6 months after transplantation in 10 patients. Median circulating naive CD4 counts were 44 × 10^6/L (range, 11-440 × 10^6/L) and 200 × 10^6/L (range, 5-310 × 10^6/L) at 12 and 24 months after transplantation and T-cell receptor excision circles were 2,238/10^6 T cells (range, 320-8,807/10^6 T cells) and 4,184/10^6 T cells (range, 1,582-24,596/10^6 T cells). Counts did not usually reach normal levels for age, but patients were able to clear pre-existing infections and those acquired later. At a median of 49 months (range, 22-80 months), 8 have ceased prophylactic antimicrobials and 5 have ceased immunoglobulin replacement. Histologic confirmation of thymopoiesis was seen in 7 of 11 patients undergoing biopsy of transplanted tissue, including 5 showing full maturation through to the terminal stage of Hassall body formation. Autoimmune regulator expression was also demonstrated. Autoimmune complications were seen in 7 of 12 patients. In 2 patients early transient autoimmune hemolysis settled after treatment and did not recur. The other 5 experienced ongoing autoimmune problems, including thyroiditis (3), hemolysis (1), thrombocytopenia (4), and neutropenia (1).

Conclusions: This study confirms the previous reports that thymus transplantation can reconstitute T cells in patients with

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CASE REPORT

AJT

Correction of both immunodeficiency and hypoparathyroidism by thymus transplantation in complete DiGeorge syndrome

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Combined immune deficiency due to athymia in patients with complete DiGeorge syndrome can be corrected by allogeneic thymus transplantation. Hypoparathyroidism is a frequent concomitant clinical problem in these patients, which persists after thymus transplantation. Cotransplantation of allogeneic thymus and parental parathyroid tissue has been attempted but does not achieve durable correction of the patients' hypoparathyroidism due to parathyroid graft rejection. Surprisingly, we observed correction of hypoparathyroidism in one patient after thymus transplantation. Immunohistochemical analysis and fluorescence in situ hybridization confirmed the presence of allogeneic parathyroid tissue in the patient's thymus transplant biopsy. Despite a lack of HLA-matching between thymus donor and recipient, the reconstituted immune system displays tolerance toward the thymus donor. Therefore we expect this patient's hypoparathyroidism to be permanently cured. It is recognised that ectopic parathyroid tissue is not infrequently found in the thymus. If such thymuses could be identified, we propose that their use would offer a compelling approach to achieving lasting correction of both immunodeficiency and hypoparathyroidism.

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REVIEW
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Current and Future Therapeutic Approaches for Thymic Stromal Cell Defects

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Inborn errors of thymic stromal cell development and function lead to impaired T-cell development resulting in a susceptibility to opportunistic infections and autoimmunity. In their most severe form, congenital athymia, these disorders are life-threatening if left untreated. Athymia is rare and is typically associated with complete DiGeorge syndrome, which has multiple genetic and environmental etiologies. It is also found in rare cases of T-cell lymphopenia due to Nude SCID and Otofaciocervical Syndrome type 2, or in the context of genetically undefined defects. This group of disorders cannot be corrected by hematopoietic stem cell transplantation, but upon timely recognition as thymic defects, can successfully be treated by thymus transplantation using cultured postnatal thymic tissue with the generation of naïve T-cells showing a diverse repertoire. Mortality after this treatment usually occurs before immune reconstitution and is mainly associated with infections most often acquired pre-transplantation. In this review, we will discuss the current approaches to the diagnosis and management of thymic stromal cell defects, in particular those resulting in athymia. We will discuss the impact of the expanding implementation of newborn screening for T-cell lymphopenia, in combination with next generation sequencing, as well as the role of novel diagnostic tools distinguishing between hematopoietic and thymic stromal cell defects in facilitating the early consideration for thymus transplantation of an increasing number of patients and disorders. Immune reconstitution after the current treatment is usually incomplete with relatively common inflammatory and autoimmune complications, emphasizing the importance for improving strategies for thymus replacement therapy by optimizing the current use of postnatal thymus tissue and developing new approaches using engineered thymus tissue.

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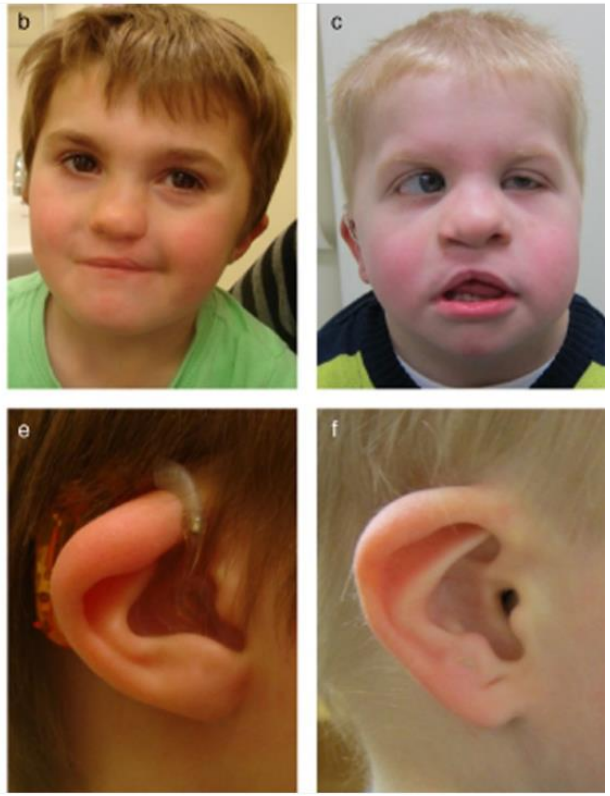
T-cell lymphopenia due to complete DiGeorge syndrome, Nude SCID and Otofaciocervical Syndrome type 2, or in the context of genetically undefined defects. This group of disorders cannot be corrected by hematopoietic stem cell transplantation, but upon timely recognition as thymic defects, can successfully be treated by thymus transplantation using cultured postnatal thymic tissue with the generation of naïve T-cells showing a diverse repertoire. Mortality after this treatment usually occurs before immune reconstitution and is mainly associated with infections most often acquired pre-transplantation

- **CHARGE syndrome:**
- Autosomal dominant disorder with a prevalence of one in 10 000.
- The *CHD7* gene is mutated in most of the cases, mutations in the *Semaphorin-3E* gene in a smaller proportion
- Most cases are sporadic, in rare instances, transmission from a mildly affected parent has been reported.
- CHARGE syndrome: Coloboma, Heart malformation, Choanal Atresia, Retardation of growth and / or development, Genital anomalies, and Ear anomalies.
- New frequent clinical finding are: dysmorphic features, rhombencephalic dysfunction, hypoplasia of the semicircular canals and archinencephaly.

TABLE 1 Prevalence of clinical features in individuals with CHARGE syndrome with a confirmed pathogenic *CHD7* variant

Feature	Lalani 2006 *N* = 64% (positive/observed)	Zentner 2010[a] *N* = 123% (positive/observed)	Bergman 2011 *N* = 280% (positive/observed)	Combined %
External ear anomaly	95 (59/62)	90 (95/106)	97 (224/231)	95
Semicircular canal anomaly	95 (21/22)	95 (37/39)	94 (110/117)	94
Coloboma	89 (55/62)	75 (85/114)	81 (189/234)	80
Choanal atresia	60 (34/57)	35 (39/113)	55 (99/179)	49
Cleft lip and/or palate	30 (18/60)	32 (35/108)	48 (79/163)	40
Cranial nerve dysfunction (VII, VIII, others)	92[b] (54/59)	85[b] (80/94)	99 (173/174)	94
Feeding difficulties			82 (90/110)	82
Facial palsy	64 (36/56)	35 (19/55)	66 (80/121)	58
Anosmia			80 (24/30)	80
Genital hypoplasia	55 (29/53)	57 (61/107)	81 (118/145)	68
Congenital heart defect	92 (54/59)	75 (86/115)	76 (191/252)	78
Tracheo-esophageal anomaly	18 (10/55)	22 (16/72)	29 (42/146)	25
Developmental delay			99 (147/149)	99
Intellectual disability		76 (64/84)[c]	80 (108/135)	79
Growth retardation		68 (65/96)	36 (35/94)	55



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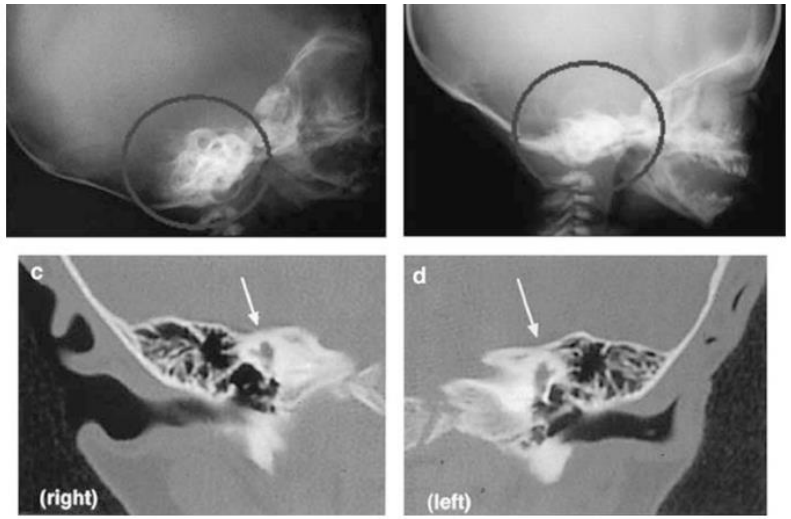
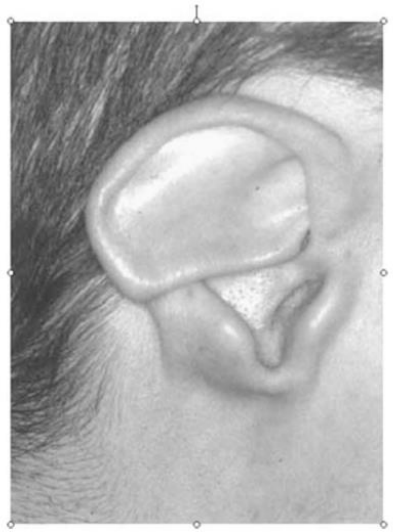
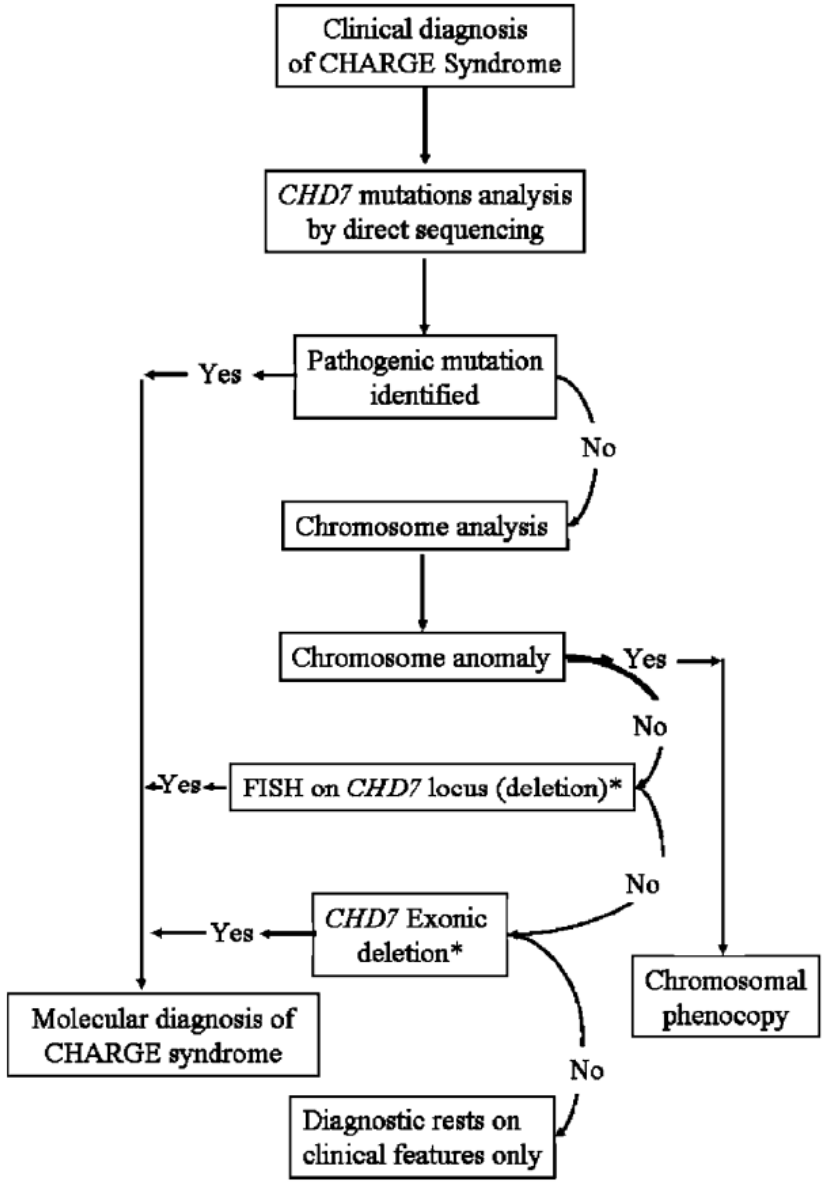


Figure 3 (a) Profile view of normal newborn skull. The semicircular canals are densely mineralized, bulging over the petrous bone (circle). (b) Profile of the skull in an affected newborn. Note absence of the canals. (c–d) Computerized tomography scan of the inner ear of an affected child, revealing absence of the canals.



Typical cup-shaped aspect of 'CHARGE ear'.



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- CHARGE syndrome is a disorder with highly variable phenotypes depending on the mutated gene and the individual's general condition.
- The proposed treatment depends on the phenotype and the affected organ.
- discovering therapeutic targets for CHARGE syndrome is directed toward identification of the cellular and biochemical signaling pathways and mechanisms that are disrupted with CHD7 deficiency.
  - One successful example of this has been a report showing that changes in retinoic acid signaling can partially rescue Chd7 loss of function phenotypes in the inner ear and brain (Micucci et al., 2014)
  - inhibition of Topoisomerase rescues cerebellar defects in Chd7 mutant mice (Feng et al., 2017)
  - inhibition of Reelin, a glycoprotein target of CHD7, corrects Chd7 mutant mouse cerebellar granule cell abnormalities(Whittaker et al., 2017)

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INTRODUCTION

WILEY AMERICAN JOURNAL OF medical genetics Seminars in Medical Genetics

New insights and advances in CHARGE syndrome: Diagnosis, etiologies, treatments, and research discoveries

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CHARGE syndrome is a multiple congenital anomaly condition caused, in a majority of individuals, by loss of function pathogenic variants in the gene *CHD7*. In this special issue of the *American Journal of Medical Genetics part C*, authors of eleven manuscripts describe specific organ system features of CHARGE syndrome, with a focus on recent developments in diagnosis, etiologies, and treatments. Since 2004, when *CHD7* was identified as the major causative gene in CHARGE, several animal models (mice, zebrafish, flies, and frog) and cell-based systems have been developed to explore the underlying pathophysiology of this condition. In this article, we summarize those advances, highlight opportunities for new discoveries, and encourage readers to explore specific organ systems in more detail in each individual article. We hope the excitement around innovative research and development in CHARGE syndrome will encourage others to join this effort, and will stimulate other investigators and professionals to engage with individuals diagnosed as having CHARGE syndrome, their families, and their care providers.

there are many challenges that need to be overcome before any of these pre-clinical research discoveries can be translated into clinical trials. First, the accurate and effective delivery of replacement genes, corrective genes, or pharmacological agents requires that they not induce major off-target effects.

Second, any gene replacement strategy would need to demonstrate lack of toxicity and high tropism for relevant cells and tissues.

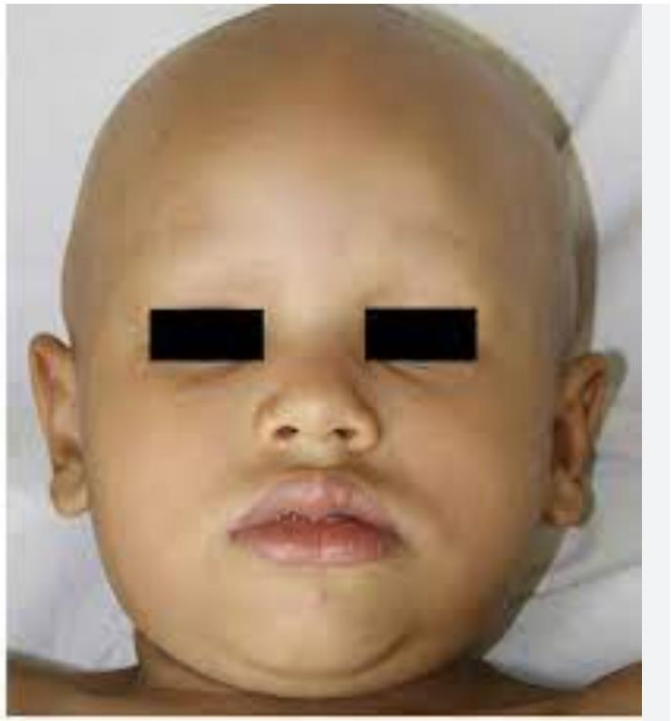
Third, therapies aimed at early embryonic time points would need to be administered in utero and lack adverse effects on the mother.

- **FOXN1 deficiency**:
- T-B+NK+ severe combined immunodeficiency:
- autosomal recessive
- This gene encodes a transcription factor essential for the development of the thymus, the primary lymphoid organ that supports T-cell development and selection

The clinical triad of :

- absent thymus(resulting in severe T-cell immunodeficiency)
- congenital alopecia universalis
- nail dystrophy
- Diagnosis relies on testing for LOF in the FOXN1

- Treatment: HLA-matched genoidentical hematopoietic cell transplantation or thymus tissue transplantation
- Early diagnosis, supportive care and definitive management result in better patient outcomes.
- Without these the prognosis is poor due to early-onset life threatening infections.



ARTICLE

Heterozygous *FOXN1* Variants Cause Low TRECs and Severe T Cell Lymphopenia, Revealing a Crucial Role of FOXN1 in Supporting Early Thymopoiesis

Marita Bosticardo,[1] Yasuhiro Yamazaki,[1] Jennifer Cowan,[2] Giuliana Giardino,[3] Cristina Corsino,[1] Giulia Scalia,[4] Rosaria Prencipe,[3] Melanie Ruffner,[5] David A. Hill,[5] Inga Sakovich,[6] Irma Yemialyanava,[6] Jonathan S. Tam,[7] Nurcicek Padem,[8] Melissa E. Elder,[9] John W. Sleasman,[10] Elena Perez,[11] Hana Niebur,[12] Christine M. Seroogy,[13] Svetlana Sharapova,[6] Jennifer Gebbia,[14] Gary Ira Kleiner,[14] Jane Peake,[15] Jordan K. Abbott,[16] Erwin W. Gelfand,[16] Elena Crestani,[17] Catherine Biggs,[17,18] Manish J. Butte,[19] Nicholas Hartog,[20] Anthony Hayward,[21] Karin Chen,[22] Jennifer Heimall,[5] Filiz Seeborg,[23] Lisa M. Bartnikas,[17] Megan A. Cooper,[24] Claudio Pignata,[3,25] Avinash Bhandoola,[2,25] and Luigi D. Notarangelo[1,25,*]

FOXN1 is the master regulatory gene of thymic epithelium development. FOXN1 deficiency leads to thymic aplasia, alopecia, and nail dystrophy, accounting for the nude/severe combined immunodeficiency (nu/SCID) phenotype in humans and mice. We identified several newborns with low levels of T cell receptor excision circles (TRECs) and T cell lymphopenia at birth, who carried heterozygous loss-of-function *FOXN1* variants. Longitudinal analysis showed persistent T cell lymphopenia during infancy, often associated with nail dystrophy. Adult individuals with heterozygous *FOXN1* variants had in most cases normal $CD4^+$ but lower than normal $CD8^+$ cell counts. We hypothesized a *FOXN1* gene dosage effect on the function of thymic epithelial cells (TECs) and thymopoiesis and postulated that these effects would be more prominent early in life. To test this hypothesis, we analyzed TEC subset frequency and phenotype, early thymic progenitor (ETP) cell count, and expression of FOXN1 target genes (*Ccl25*, *Cxcl12*, *Dll4*, *Scf*, *Psmb11*, *Prss16*, and *Cd83*) in *Foxn1*$^{nu/+}$ (*nu*/+) mice and age-matched wild-type (+/+) littermate controls. Both the frequency and the absolute count of ETP were significantly reduced in *nu*/+ mice up to 3 weeks of age. Analysis of the TEC compartment showed reduced expression of FOXN1 target genes and delayed maturation of the medullary TEC compartment in *nu*/+ mice. These observations establish a *FOXN1* gene dosage effect on thymic function and identify *FOXN1* haploinsufficiency as an important genetic determinant of T cell lymphopenia at birth.

Introduction

The thymus is the central organ for the development of adaptive immunity, since it houses all stages of T cell differentiation from bone marrow-derived early thymic progenitors and supports the development of epithelial cells in the thymus and skin.[1–3] The earliest stages of thymus development from the third pharyngeal pouch are independent of *Foxn1* during early stages of mouse embryogenesis (E9.5–E11 days), whereas *Foxn1* expression is necessary for the development

- Both thymus transplantation and HSCT have been previously used to treat individuals with bi-allelic FOXN1 mutations and a nude phenotype.
- Three individuals received unmanipulated T cell-replete HSCT from HLA-matched siblings. Reconstitution of the T cell count was observed in one, who was reported to be alive and infection-free 6 years after transplantation; however, CD4+ T cells were unable to proliferate.
- The other two individuals who received HSCT died of complications post-transplant.
- Two individuals received thymus transplantation; both had a slower T cell reconstitution, but eventually attained normal T cell counts, with capacity to generate naive CD4þ T cells, normal in vitro T cell proliferative responses to mitogens, and reconstitution of antibody production. These subjects were reported to be alive and infection free at 3 and 5 years after transplantation, respectively, although one of them developed autoimmune hypothyroidism and vitiligo.

- **Hyper IgE syndrome:**
- Hyper IgE syndrome historically been defined by the triad of elevated IgE, dermatitis, and recurrent skin and lung infections and include diseases caused by mutations of STAT3, TYK2, PGM3, ZNF341, CARD11, and IL6ST.
- IL6ST and ZNF341 are two phenocopies of STAT3 LOF mutations

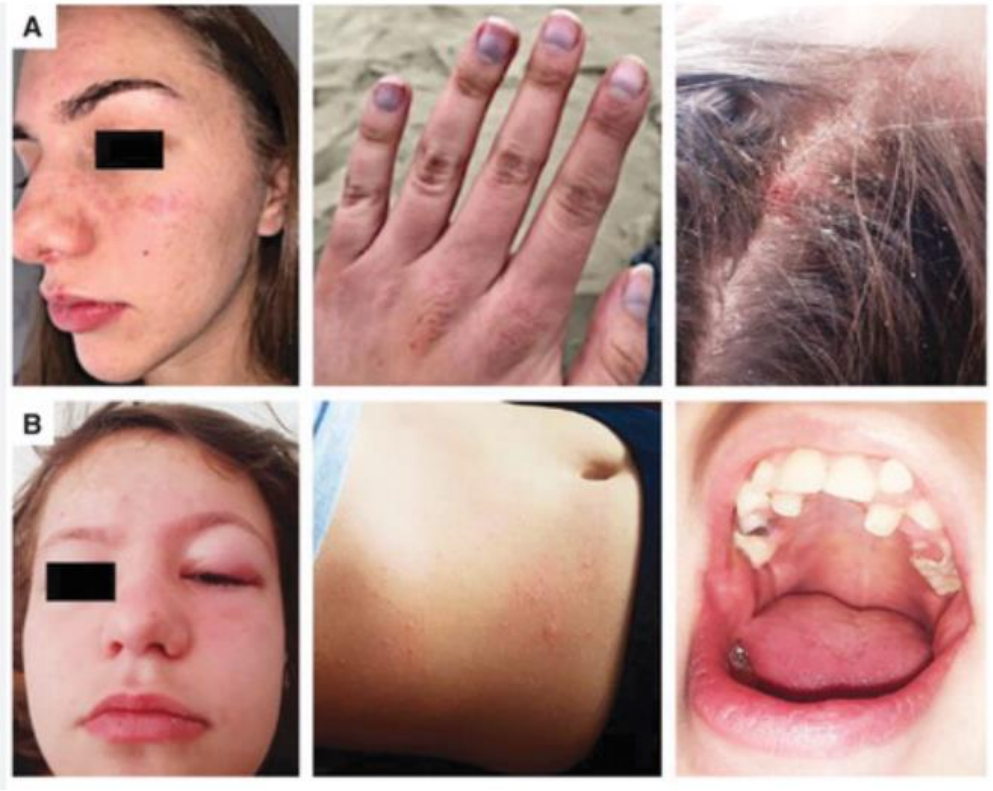
- **AD-HIES (Job syndrome)**
- Autosome dominant/ STAT3 LOF mutation
- eczema, staphylococcal and fungal skin and pulmonary infection, scoliosis and minimal trauma fractures, and vascular aneurysm, food allergy and anaphylaxis, facial features
- skin abscesses (74%), eczema (58%),drug allergy (43%), food allergy (38%), retained primary teeth (41%), fractures (39%), scoliosis (34%), cancer (7%)

- STAT3 plays a crucial role in the differentiation of naïve T cells into IL-17 producing CD4+ T cells (Th17 cells). Th17 cells are involved in the response to fungal and extracellular bacterial infections.
- reduced or absent Th17
- decrease production of IFN gamma and tumor necrosis factor (TNF) alpha, IL-9 by T cells
- decreased numbers of CD8+ memory T cells
- diminished delayed-type hypersensitivity and lymphoproliferative responses to antigenic stimulation

- Reduced memory B cells
- Decreased response to a T cell-dependent antigen
- Elevation of IgE
- Poor response to both protein and polysaccharide immunizations
- Eosinophilia

- Infections:
- abscesses, furuncles, and cellulitis, lymphadenitis, cold abscess, Staphylococcal abscesses (often on and around the face, neck, and scalp) from early infancy
- chronic upper-airway infections with persistent and/or recurrent episodes of sinusitis, suppurative otitis media, and mastoiditis, which may require surgical intervention from 10 month old
- Pulmonary infections, most commonly due to S. aureus, are recurrent and may be life threatening.
- Opportunist pulmonary infections with Pneumocystis jirovecii and Aspergillus, Pseudomonas, and Nocardia spp.
- Lung abscesses were most commonly due to Pseudomonas aeruginosa or Aspergillus fumigatus infections

- Broad nasal bridge, frontal bossing, wide outer canthal distances, and deep-set eyes.
- The prominent forehead, lower lip, and broad nose can already be observed during infancy, but the doughy consistency of the skin takes 2-5 years to become noticeable on the face.



- Diagnosis: based upon clinical and laboratory findings with confirmation by genetic defect (eg, STAT3 pathogenic variant).
- Management:
  - Treating eczema
  - Prophylaxis antibiotics
  - Treatment of infections
  - IGRT in hypogammaglobulinemia
- Hematopoietic cell transplantation (HCT)
  - Early attempts of hematopoietic cell transplantation (HCT) for HIES did not demonstrate long-term benefit.
  - Subsequently, two patients with HIES with severe, recurrent pulmonary infections and non-Hodgkin lymphoma who underwent HCT benefit over 10 and 14 years of follow-up.

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ORIGINAL ARTICLE

Hematopoietic Stem Cell Transplantation Resolves the Immune Deficit Associated with STAT3-Dominant-Negative Hyper-IgE Syndrome

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Abstract

Autosomal dominant hyper-IgE syndrome caused by dominant-negative loss-of-function mutations in signal transducer and activator of transcription factor 3 (*STAT3*) (STAT3-HIES) is a rare primary immunodeficiency with multisystem pathology. The quality of life in patients with STAT3-HIES is determined by not only the progressive, life-limiting pulmonary disease, but also significant skin disease including recurrent infections and abscesses requiring surgery. Our early report indicated that hematopoietic stem cell transplantation might not be effective in patients with STAT3-HIES, although a few subsequent reports have reported successful outcomes. We update on progress of our patient now with over 18 years of follow-up and report on an additional seven cases, all of whom have survived despite demonstrating significant disease-related pathology prior to transplant. We conclude that effective cure of the immunological aspects of the disease and stabilization of even severe lung involvement may be achieved by allogeneic hematopoietic stem cell transplantation. Recurrent skin infections and abscesses may be abolished. Donor T_H17 cells may produce comparable levels of IL17A to healthy controls. The future challenge will be to determine which patients should best be offered this treatment and at what point in their disease history.

Keywords Autosomal dominant hyper IgE syndrome · dominant-negative STAT3 mutations · hematopoietic stem cell transplantation · Job syndrome · STAT3-HIES T_H17 cells

- **Zinc finger 341 deficiency:**
- ZNF341 is a transcription factor that resides in the nucleus, where it binds a specific DNA motif present in various genes, including, most notably the STAT3 promoter. The patients' cells have low basal levels of STAT3 mRNA and protein.
- **IL6ST:**
- Twelve patients suffer from cold staphylococcal lesions and mucocutaneous candidiasis, severe allergy, and skeletal abnormalities with DN mutation in IL6ST, phenocopy of STAT3 LOF mutation.
- DN STAT3 and IL6ST mutations appear to underlie clinical phenocopies through impairment of the IL-6 and IL-11 response pathways.

Thank you for your attention