Regional perspective on inherited immune disorders

ATMF/IPFA Joint Webinar

Day 3: October 1st, 2021

Assessment Plans to meet national requirements of human plasma-derived medicinal products

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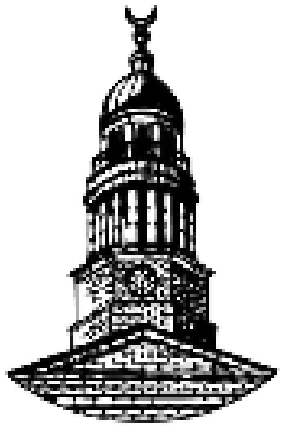
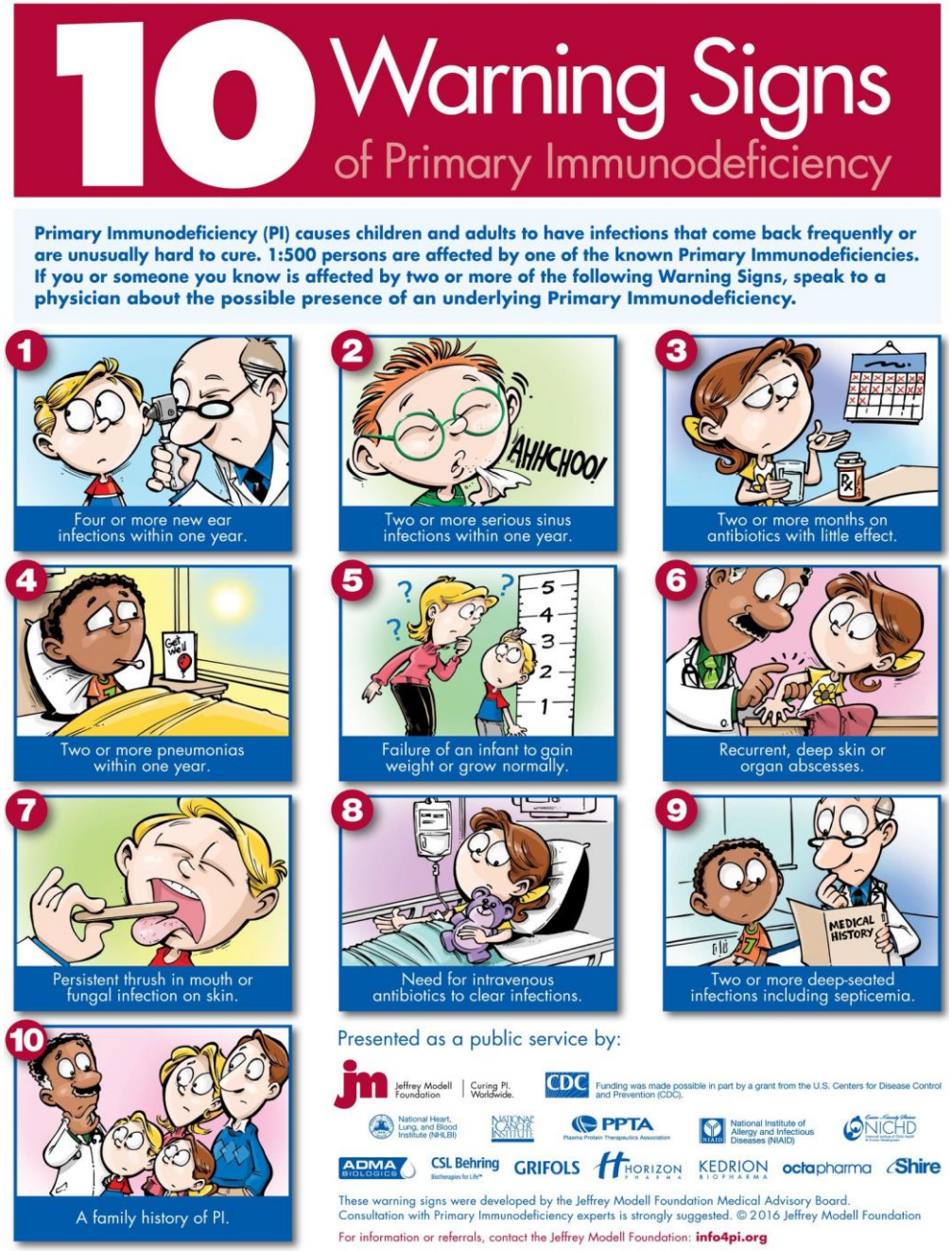
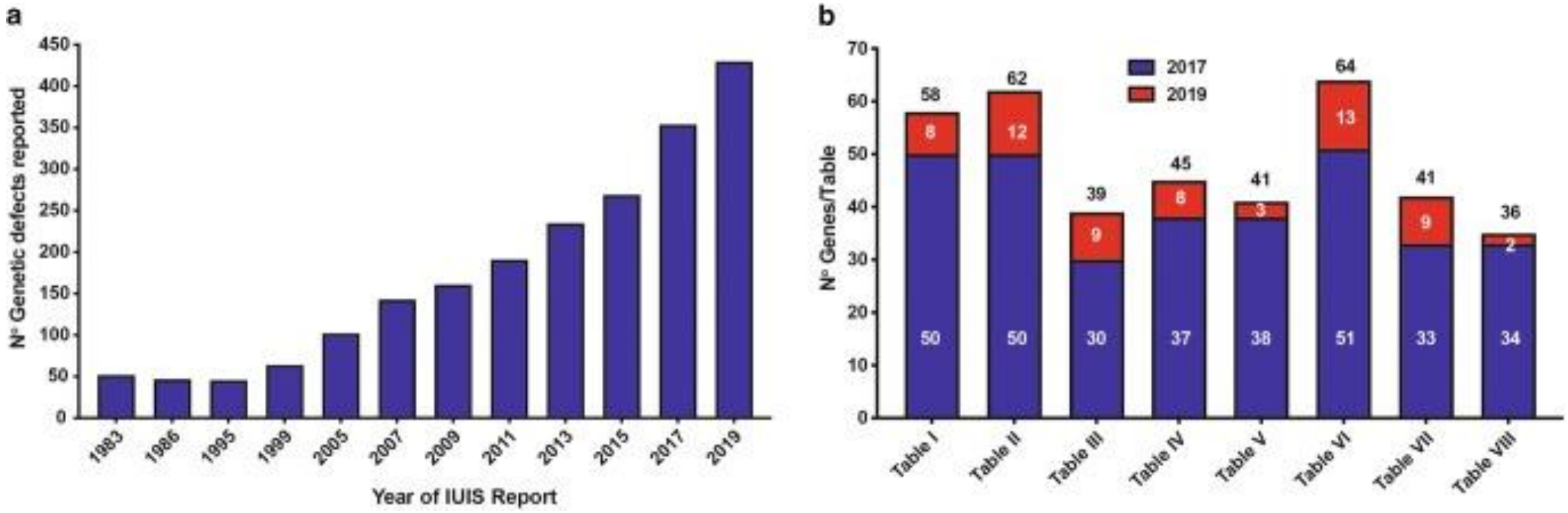


Nothing to disclose

What is PID/IEI ?

- Primary immunodeficiency diseases (PID) Human Inborn Errors of Immunity (IEI)
  - Heterogenous group of monogenic inborn errors of the immune system.
- PID/IEI patients suffer from:
  - severe, persistent, unusual, or recurrent infections
- Other presentations may include:
  - autoimmunity
  - lymphoproliferation and/or
  - malignancy

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What is PID/IEI ?

- In 2019, IUIS reported 406 distinct PID disorders with 430 different genes defects.
- IEI were traditionally considered to be rare diseases, affecting ~ 1 in 10,000/50,000 births.
- However, with ongoing discovery of novel IEIs and improved definition of clinical phenotypes the collective prevalence of these conditions is more likely to be at least 1/1000-5000.

IUIS Classification of human IEI (2019)
[IEI = Inborn Errors of Immunity]

1.	**Combined T-cell and B-cell immunodeficiencies**	**320**
2.	**Combined immunodeficiencies with syndromic features**	**55**
3.	**Predominantly antibody deficiencies**	**33**
4.	Congenital defects of phagocytes (number and/or function)	285
5.	Defects in innate immunity	64
6.	Auto-inflammatory diseases	
7.	**Complement deficiencies**	
8.	**Immune dysregulation disorders**	**68**
9.	Phenocopies of inborn errors of immunity	
10.	**Bone Marrow Failure syndromes**	

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- **PID disorders are remarkably underreported in developing countries:**
  - **attribution of infections to malnutrition**
  - **difficulties with diagnosis**
  - **lack of national registries**
- **With the high consanguinity rate in Egypt (~ 59.9% in rural areas), the incidence and diversity of PIDDs are expected to be very high.**

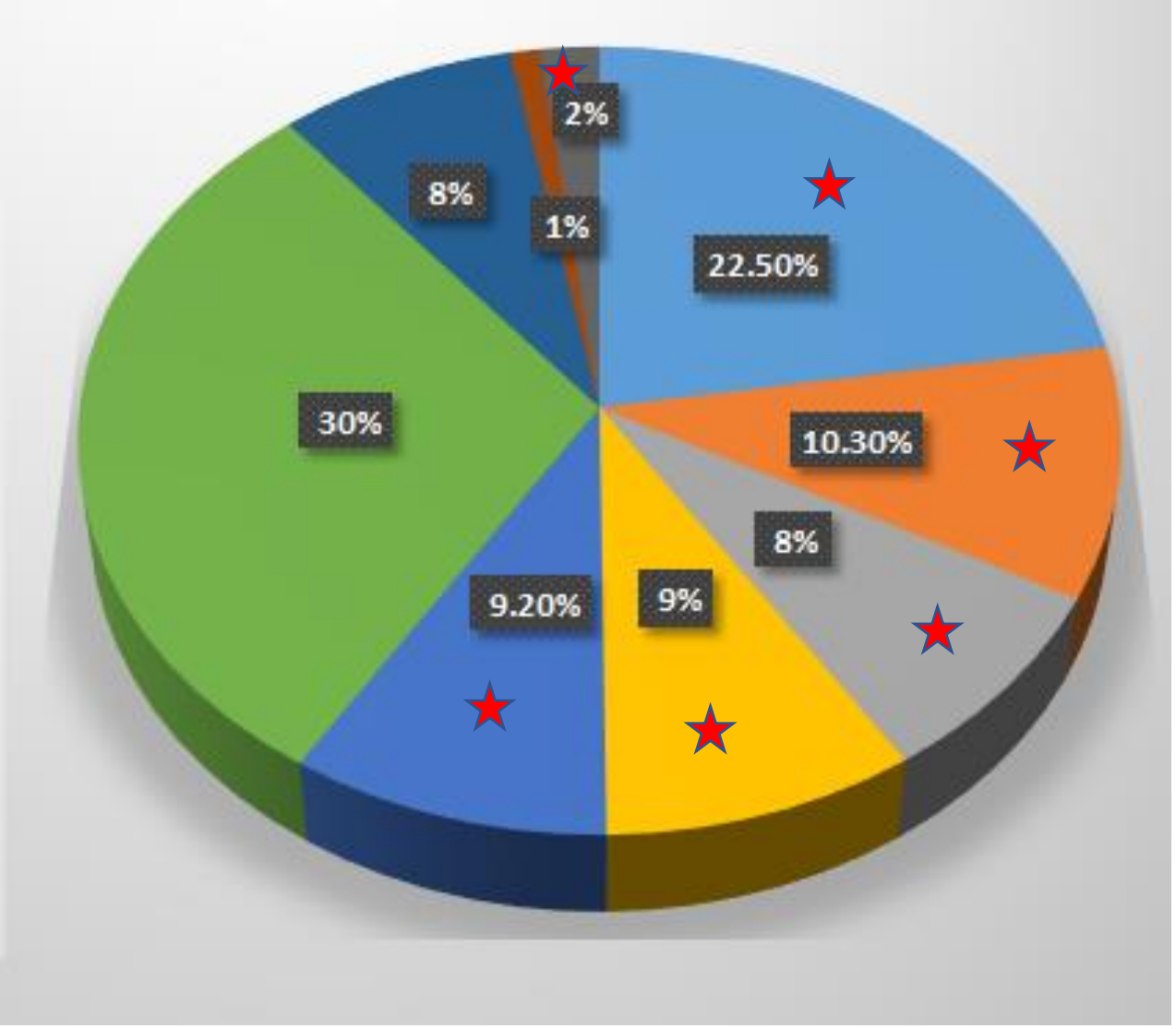
Current situation

In 2021:

- **1473 patients are being followed at the Cairo University (CU) PID center (as far north as Alexandria and south as Aswan and east as the Sinai, and from Sudan, Libya, Syria, and Yemen).**
- **483 were diagnosed with FMF & 13 with CF.**
- **977 were diagnosed with other PID disorders.**
- **Genetic defect was detected in 28.5% (71 genes).**
- **~75% were classified into one of the IUS categories based on FCM.**
- **The rate of diagnosis is almost triple compared to 2014**

Main categories of PID in Egypt 2021

- ID of cellular & humoral immunity: a.SCID
- ID of cellular & humoral immunity: b.CID less profound than SCID
- CID with Syndromic features
- Predominantly Ab defect
- Immunedysregulation
- Cong phagocytes defect
- Defects in innate immunity
- Complement deficeincy
- BM Failure



X-LA / agammaglobulinemia	• Ig replacement / 3-4 wks Mandatory – Lifetime -
Hypogammaglobulinemia / CVID	• Ig replacement /3-4 wks (400-700mg/kg) • May require Ig immunomodulatory dose (1-2 g/kg) • May require intervention specific to cytopenias • Must be categorized further to establish the molecular defect
WAS / Wiskott Aldrich Syndrome	• Often require Ig immunomodulatory dose (1-2 g/kg) • Often require intervention specific to cytopenias • HSCT or Gene therapy is the definitive therapy
Immunedysregulation: LRBA – DOCK8 – CTLA4	• Often require Ig immunomodulatory dose (1-2 g/kg) • Often require intervention specific to cytopenias • Specific immunomodulatory therapy to control the flare • HSCT or other specific therapy is required
HLH Hemophagocytic Lympho-Histiocytosis	• Often require Ig immunomodulatory dose (1-2 g/kg) • Often require intervention specific to cytopenias • Specific immunomodulatory therapy to control the flare • HSCT therapy is the definitive therapy
Bone Marrow failure syndromes	
SCID / CID	• Ig replacement therapy: before, during, after HSCT

♂ – 15y – no consanguinity

- Family history: 2 previous male sib deaths
  - One ♂ died at 1 ½ y: prolonged fever – hepatosplenomegaly – died in hospital
  - One ♂ died at 3 ½ y: fever – jaundice – sudden hepatomegaly – coma – died in hospital
- At 10 y:
  - Unremitting fever – Hepatosplenomegaly – generalized LN enlargement
  - CT Chest:
    - Lt lower lung lobe: consolidation-collapse
    - Mediastinal & Axillary LN enlargement
  - Treated with IV antibiotics for several months – then Lobectomy was performed
- Jan 2020 (15y): severe COVID19 – coma – ventilated for 1 wk
- March 2020: referred to PID Unit for evaluation

♂ – 15y – no consanguinity – 2 ♂ sib deaths

- CBC: normal leucocytosis during infection episodes (22,000/dl)
- Lymphocyte subsets (FACS): normal % and absolute counts
  - CD19 (B lymphocytes): 9.6% [6-32%]
- Ig quantitation:
  - IgG: **173** mg/dl [639-1349]
  - IgM: **12** mg/dl [56-152]
  - IgA: **39** mg/dl [70-312]
- Patient started IVIG replacement therapy/monthly + oral antibiotics

♂ – 16y – no consanguinity – 2 ♂ sib deaths

- Because we thought that a further definitive diagnosis is required
  - NGS panel sequencing (60 gene panel for CVID & immunedysregulation disorders) was performed at Cairo University Children PID Lab

NGS (Cairo Univ – June 2021):

XLP1 (X-linked Lympho-proliferative disease type I)

Mutation in the *SH2D1A* gene – Hemizygous - pathogenic

c.245dupA, (p.Asn82LysfsTer22)

July 2021: referred for HSCT

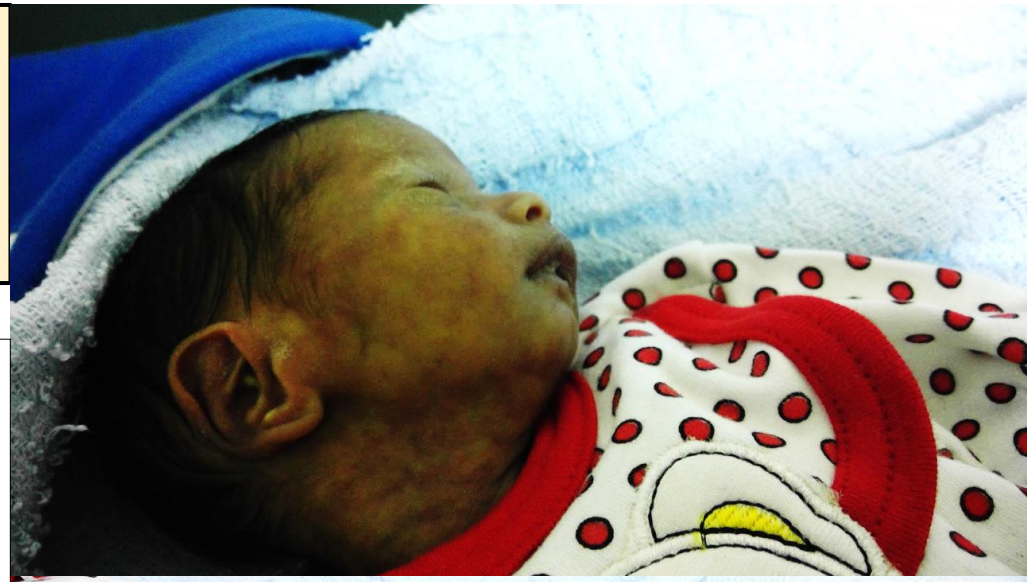
XLP-1

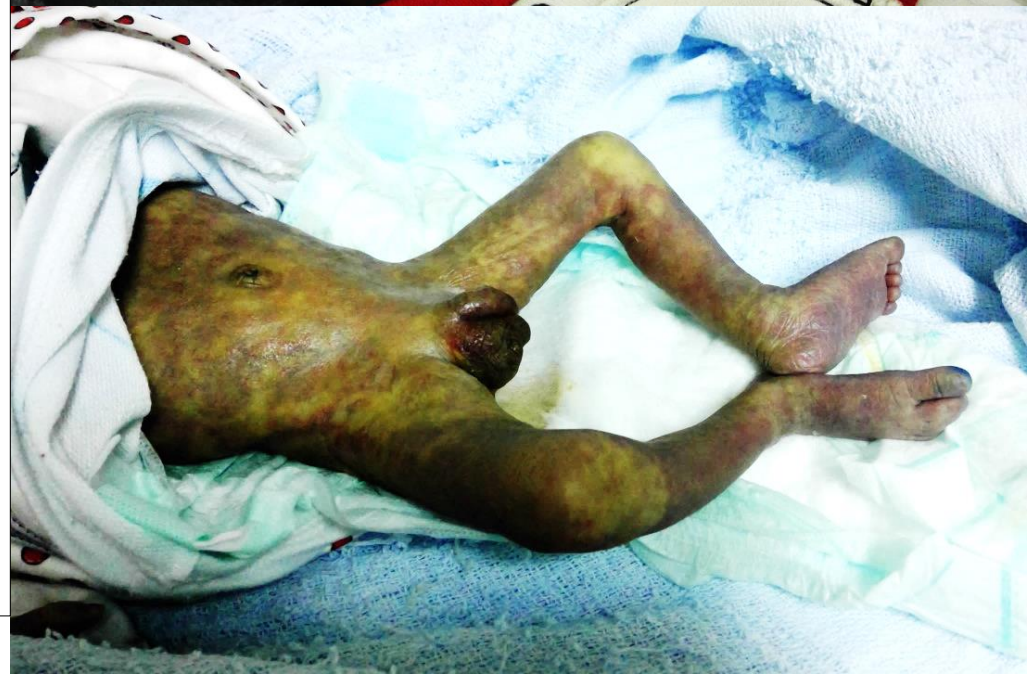
- an increased risk to develop a severe fulminant infectious mononucleosis (EBV)
- EBV infection usually progresses to fatal HLH
- X-linked lymphoproliferative type 1 (XLP-1) patients are at risk of:
  - lymphoma
  - hypogammaglobulinemia
  - aplastic anemia
  - Vasculitis: lungs, eyes, brain or other organs

Ig replacement / Transfusions for PID patients can be very problematic

SCID

- ♂ – 11d – consanguineous parents
- NICU: LBW – Bilirubin: 19.5 mg/dl [D1]
- Exchange blood transfusion
- 4 d later: Jaundice – thrombocytopenia
- **CD3:** **0.5%** **CD4:** **0.1%** **CD8:** **0.4%**
- **CD19:** **0.6%**
    - **GVHD – post transfusion**





M – 3 y -

- Severe napkin dermatitis
- At 1 y: pneumonia
- At 18m: pneumonia with pleural effusion
- Onychomycosis
- LL: cellulitis & abscess formation
- Persistent lymphopenia (1,200)
- Persistent CD4 lymphopenia (9%)
- Normal Immunoglobulins level
- WES: RAG1/SCID

♂ – 3 y – Atypical SCID/RAG1 – IVIG experience

- 26/11/2016:
  - Fever – Coomb's+ve autoimmune hemolytic anemia
  - IVIG: 2g/kg – recovered
- 26/12/2016:
  - Received 2nd monthly IVIG (replacement therapy – preparation for HSCT)
- 5/1/2017: Extreme pallor
- One month later, following his 3rd IVIG dose: acute pallor – Hb:3g/dl – very difficult to match
- IVIG was stopped
- Patient travelled in order to perform HSCT – he was given cautiously SCIG

Conclusion:

- PID/IEI is not uncommon in Egypt
- Improved diagnostic procedures, including genetic diagnosis has greatly improved our understanding of those life-threatening disorders
- Several PID patients are very dependent on blood products as well as immunoglobulin transfusions
- Transfusions in PID patients, though essential, may carry many risks of complications
- Immunoglobulin replacement therapy is an essential treatment for many PID patients:
  - It must be carried out under supervision of personnel acquainted with the procedure
  - Several Immunoglobulin preparations ought to be available for use

Thanks