WHEN DO WE HAVE TO THINK ABOUT PRIMARY IMMUNODEFICIENCY?

CÂND TREBUIE SĂ NE GÂNDIM LA IMUNODEFICIENȚA PRIMARĂ?

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Summary

Primary immunedeficiencies (PIDs) are rare disorders, with discordant statistics regarding their reported prevalence (dependent on population, country, PID center): 1.51/100,000 (Germany), 4.97/100,000 (France), 12.4/ 100,000(Australia), 10/100,000 (worldwide), 80-100/ 100, 000 inhabitants (EDQM). It is estimated that 1% of the global population has PID and > 6 million persons suffer from PID worldwide, 70-90% of them remaining undiagnosed (I. Meyts, 2021; JM Boyle, 2007).

Rezumat

Imunodeficiențele primare (IDP) sunt tulburări rare, cu statistici discordante în ceea ce privește prevalența raportată (în funcție de populație, țară, centru PID): 1,51/100.000 (Germania), 4,97/100.000 (Franța), 12,4/ 100.000 (Australia), 10/100.000 (în toată lumea), 80-100/ 100.000 locuitori (EDQM). Se estimează că 1% din populația globală are BIP și > 6 milioane de persoane suferă de BIP la nivel mondial, 70-90% dintre ele rămânând nediagnosticate.

INTRODUCTION

PIDs are genetic disorders related to more than 485 identified genes, with a heterogenous expression, in form of more than 430 phenotypically different pathological entities (S. Tangue, 2022). They are most severe diseases, with markedly increased vulnerability to infections, auto-immunity, allergy, inflammation, or cancer with high mortality rates. PID is a real challenge to healthcare systems because of a large range of conditions: low level of awareness, lack of expert physicians, and expensive, sophisticated diagnosis tools and treatment.

Patients with PIDs are the subject of medical interest only for less than a half-century, rea-ching today a new era with a “decade of progress and a promising future”. Huge advances suc-ceeded with adequate care to improve life expectancy and quality of life. They are candidates for “functional cure” or even “phenotypic, genetic cure”. (I.Meyts-2021). Early, timely, appropriate diagnosis ensures 95% chance of a “functional” cure or long-term survival. Severe combined immunodeficiencies (SCID) are “immunological emergencies” that require urgent intervention. It has in 80% of cases a chance of “functional cure” if the diagnosis is established in time (first 1-2 months of age). (S. Tangue- 2022)

CALL FOR INITIATION AND CONSOLIDATION OF PREDICTIVE DATA FOR PID DIAGNOSIS

Taking all these into consideration, as active members of the J Project and Jeffrey Modell project, related to Immunopedia, we considered of interest aiming for a proper, timely PID diagnosis, to focus our attention on diagnosis predictions for these disorders.

Clinical predictors for diagnosis

The most used clinical predictors are the ten warning signs proposed by the advisory board of the Jeffrey Modell Foundation, initiated for general practitioners, mainly pediatricians, in 1990. (Tab.1)

Table 1. Ten warning signs of primary immunodeficiency (children)

1	≥4 ear infections in one year
2	≥2 serious sinus infections in one year
3	≥2 pneumonias in one year
4	Recurrent, deep skin or organ abscesses
5	Persistent thrush in the mouth or fungal infection on the skin
6	≥2 deep-seated infections including septicemia
7	≥2 months on antibiotics with little effect
8	Need for intravenous antibiotics to clear infections
9	Failure of an infant to gain weight or grow normally
10	Family history of primary immunodeficiency

(JM Foundation-advisory board – 1990)

Used in clinical practice, along the time, it has become evident that the sensitivity and specificity of these signs are not optimal. (Tab. 2, 3)

Table 2. The 10 JM warning signs for PID (children)

Variables	Arkwright PD, Gennery AR –(2011)	Peters Lankirsch-(2019)	F.Pinto-Mariz-(2021)	Shereen Reda (2013)
Sensitivity for early diagnosis	56%	inadequate	60-70%	94%
Specificity for early diagnosis	16%	Insufficient	-	69%
				Prediction for PID; family history, sibling death, parental consanguinity, atopy, autoimmunity, malignancy

Table 3. Frequency (percentage) of ≥2 warning signs in children with and without PID

	<2 warning signs	≥2 warning signs	Relative risk (95% CI) compared with no PID
No PID	70 (52%)	63 (48%)	-
Any PID	163 (38%)	267 (62%)*	1.8 (1.2-2.7)
Neutrophil PID	10 (14%)	63 (86%)*	7.0 (3.3-14)
Complement PID	9 (41%)	13 (59%)	1.6 (0.6-4.0)
B cell PID	42 (40%)	63 (60%)	1.7 (1.0-2.8)
T cell PID	102 (44%)	128 (56%)	1.4 (0.9-2.1) *<p0,01

(Peter Arkwright, Andrew Gennery -2011)

The JM score remained of utmost importance for general pediatric practitioners, increasing their awareness of this disorder group. But it is often facing difficulties and barriers for an early diag-nosis. Therefore, physicians working in immunology departments underlined the importance of some other clinical data with diagnosis value: chronic diarrhea, consanguinity, family history of TBC, sibling death, and complications due to live vaccines (Tab 4,5).

Table 4. JMF score in PID/ SCID vs CG

PID	SID	CG	p
3,36 ± 1,65	3,72 ± 1,12	0,34 – 0,61	<0,05
JMF warning signs useful for the early diagnosis of PID/ SID Adverse factors not included: -parental consanguinity -chronic diarrhea -family history of TBC			

(Fadime Ceyda Eldeniz (2022)

Table 5. Complications due to live attenuated vaccines

Disseminated BCG (Mycobacterium Bovis, Bacillus Calmette-Guerin)
Poliomyelitis due to poliovirus vaccine
Diarrhea due to the rotavirus vaccine
Varicella post vaccine

(Beatriz Tavares Costa – Carvalho -2014)

The warning signs connected to infectious complications have been extended to the nature of their etiological agents. There was observed a special profile of these agents respon-sible for the complications in PID. (Tab.6, 7)

Table 6. Warning signs of PID for infectious disease specialists

Clinical occurrences
Recurrent or persistent Cryptosporidium, Isospora, Giardiasis
Persistent fever of unknown origin
Infections from extracellular bacteria
Infections due to Neisseria meningitis
Infection from S. aureus and gram-negative bacteria: Serratia marcescens, Burkholderia cepacian and gladioli, Nocardia spp, Chromobacterium violaceum, Granulobacter bethesdensis
Infection from fungi: Pneumocystis jiroveci, Aspergillus and Candida albicans
Infection by atypical Mycobacteria/ Salmonella and/ or Bacillus Calmette-Guerin side effects; Paracoccidioides sp, Leishmania, Cryptococcus
Infections from Herpes virus
Fulminant or chronic infection by Epstein-Barr virus
Infections of the central nervous system (CNS): meningococcal meningitis, herpes encephalitis, fungal infections

(Beatriz Tavares Costa – Carvalho -2014**)**

Table 7. Uncommon infections agents in PID

Uncommon infections or uncommon presentations in HIV-negative patients	Infections agents in chronic diarrhea
Atypical mycobacteriosis	Enteroviruses
Tuberculosis resistant infection	Rotavirus
Histoplasmosis	Recurrent giardiasis
Neurocryptococcosis	Campylobacter
Aspergillosis	Cryptosporidium
Leishmaniasis	Persistent Salmonella
Blastomycosis	Clostridium difficile
More relevant signs in developed countries or non-endemic countries for these diseases	

(Beatriz Tavares Costa – Carvalho -2014)

It is worth noting, that the difficulties encountered in the real life:

- 20% of PID patients without infection at presentation and consequently not included for PID investigation
- 60% of patients not diagnosed until adulthood
- 70% hospitalized prior to diagnosis vs 48% post-diagnosis, encouraged the experts in immu-nology, to update the warning signs and to enlarge them with dates reflecting the non-infectious expression of PID. (I. Meyts-2021)

What to look for beyond infection?

Call for an integrative and multidisciplinary approach.

The list of predictive signs for PID has been enlarged (Tab.8,9). There have been added other clinical manifestations (hematological, gastrointestinal, dermatological, aso) and also some simple exploratory, largely accessible data like lymphopenia, hypocalcemia, and absence of thymic shadow on X-Ray. (F. Pinto-Martz,2021)

Table 8. 12 warning signs of primary immunodeficiency (newborns)

Severe and/or persistent fungal, viral, or bacterial infections
Adverse reaction to live vaccine specially BCG
Persistent diabetes mellitus or other autoimmune and/or inflammatory manifestation
Sepsis-like clinical picture without microbial isolation
Extensive skin lesion
Persistent diarrhea
Congenital heart defects (mainly conotruncal anomalies)
Delayed umbilical cord detachment (>30 days)
Familial history of PID or early deaths caused by infection
Persistent lymphocytopenia 2,500 cells/mm3 or other cytopenias, or leukocytosis without infection
Hypocalcemia with or without seizures
Absence of thymic shadow at X-Ray

(Fernanda Pinto-Mariz-2014)

Table 9. Most reliable warning signs for PID

Family history,
IV antibiotics for sepsis,
Failure to thrive,
Chronic diarrhea,
Parental consanguinity,
Adverse reaction to live vaccines,
History of allergy,
Family history of TBC,
Sibling death.

(F. Pinto-Mariz-2020)

Usage of the Scoring system ID-related score (IDRS)

Call for mathematical statistical evaluation of data

Along with the increasing importance of ”evidence-based medicine” sustained by statistical evaluations, aiming to improve the sensibility and specificity of the data supporting the PID diagnosis, a scoring system related to immunodeficiency (IDRS) has been established. It is quantifying clinical, but also some biological data. (Tab.10)

Table 10. The unmodified IDRS scoring criteria (K. Toms-2020)

Criteria	Score	Criteria	Score
Meningococcal meningitis	3	Neutropenia	2
Sepsis, identified organism	3	Cellulitis	2
Viral meni9ngitis, identified organism	3	Lymphadenitis	2
Pneumocystosis	3	Splenomegaly	2
Bacterial meningitis, identified organism	3	Thrush/ Candidiasis	1
Viral pneumonia, identified organism	3	Other mycoses	1
Pneumococcal pneumonia	3	Otitis media	1
Bacterial pneumonia, identified organism	3	Chronic otitis	1
Pneumonia other	3	Chronic mastoiditis	1
Bronchopneumonia	3	Acute sinusitis	1
Influenza	3	Acute bronchitis	1
Bronchiectasis	3	Chronic sinusitis	1
Empyema	3	Chronic bronchitis	1
Lung abscess	2	Non-infectious gastroenteritis	1
Rectal abscess	2	Malabsorption	1
Liver abscess	2	Fever, unknown origin	1
Osteomyelitis		Loss of weight	1
Giardiasis		Failure to thrive	1
Hemolytic anemia		Enlarged lymph glands	1
Thrombocytopenia		Diarrhea	1

This IDR score increased significantly the diagnostic sensitivity and specificity ($p<0.001$) (K.Toms -2020):

- it reduced the delay in diagnosis from 34,6 months (S.Nepesov -2022) to 12,4 years in the US (A.Condino-Neto -2018),
- it increased the identified specific PID defect by 46,6% in the USA and 47,9% globally (J.Quinn -2022) and,
- it proved to be useful for both, adults and children (Urs Mucke -2017)

Educational programs for increasing awareness of PID

Call for dissemination of knowledge

The dissemination of medical and scientific data reflecting the progress registered in the diag-nosis and treatment of PID with increasing rates of survival and cure rate is of decisive impor-tance. The significantly improved awareness ($p< 0.001$) of all our colleagues, pediatricians, or general practitioners, participating in such educational training courses is supporting this action. (Tab.11,12)

Table 11. Comparison of the number and percentage of correct answers given by the surveyed physicians corresponding to their specialty.

	N. of physicians		N. of answers		Correct answers				p-value
					n	%	n	%	
	2016	2019	2016	2019	2016		2019		
Pediatricians	42	34	1302	1054	785	60.3	851	80.7	<0.0001
General practitioners	25	21	775	651	423	54.6	495	76.0	<0.0001
Pediatric subspecialists	15	12	465	372	273	58.7	294	79.0	<0.0001

(Tatyana Hariyan -2020)

Table 12. Pre- and post-implementation of the educational program

	Pre (2016)	Post (2019)	p
Physicians Awareness	58.3%	79.0	p<0.001
Pediatrician awareness	64.6%	85.1%	p<0.001

(Tatyana Hariyan, Ukraine, 2020)

CONCLUSIONS

TAKE HOME MESSAGES

1. PIDs are with an estimated incidence of 1/1,200 births (with exception of IgA deficiency 1/300-500) and a prevalence of 1/1,000 worldwide; the estimated total number is 6,000,000 million,70-97% of them not diagnosed.

2. Clinical presentation is heterogenous, and highly variable, mostly involving increased sus-ceptibility to infection, frequently with non-aggressive infectious agents, but also common excessive inflammatory responses, autoimmunity, and malignancy.

3. PID should be expected at any age, mostly in patients with a positive family history, with severe recurrent chronic complicated infections with the need for intravenous antibiotics, chronic diarrhea, failure to thrive, adverse reactions to vaccines, familial and parental consan-guinity, history of TBC, sibling death.

4. It is still lacking a comprehensive and dedicated team; the need for educational programs should be our objective in order to overcome knowledge gaps among primary care physicians, the shortage of clinically trained immunologists, or the need for clinical decision support.

5. Awareness is of utmost importance. Therefore consolidate/refine the training of clinicians, update the warning signs for PID in conformity with the present ”real world” and, assure consultation with a clinical immunologist to confirm the diagnosis and establish a treatment plan!

6. Early diagnosis is decisive for life expectancy, QoL, and the chance of functional or phenotypic, genetic “cure”.

7. Ensure newborn screening, especially in case of family history and genetic counseling in the family of PID patients.

“Lives can be saved. Access to healthcare is a basic human right” (WPIW -2021)

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