ORIGINAL ARTICLE

Prevalence of pathogenic variants of inborn errors of immunity in critically ill children admitted to the pediatric intensive care unit for sepsis: A Moroccan cohort study

Prévalence des variants pathogènes des erreurs innées de l'immunité chez les enfants admis en réanimation pédiatrique: Etude de cohorte marocaine

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Abstract

Introduction: Pediatric sepsis remains a leading cause of morbidity and mortality in Africa. Nearly half of pediatric sepsis deaths occur in previously healthy children. The role of inborn errors of immunity (IEI) in susceptibility to sepsis is yet to be identified and their prevalence amongst previously healthy children admitted to the pediatric intensive care unit (PICU) is unclear. We aimed to assess prevalence of IEI among a cohort of children admitted to the PICU for community acquired sepsis and to describe demographic, microbiological, and genetic features of this cohort.
Methods: We listed a cohort of children admitted to our PICU for sepsis from January 2021 to March 2023. Demographic data was collected, and microbiological tests were performed. Written consent was obtained and whole exome sequencing (WES) was performed after DNA extraction.
Results: Thirty cases were included. Mean age at admission was 46 months (1-180), microorganisms were identified in 20 cases (66%). Bacterial sepsis was identified in 8 cases, viral sepsis in 6 cases and fungal sepsis in 2 cases. Mean pediatric sequential sepsis related organ failure assessment (pSOFA) score at admission was 6,46 (2-18). Mechanical ventilation was necessary in 18 cases. Inotropes were used in 17 cases and renal replacement therapy initiated in 3 cases. Pathogenic variants of IEI were identified in 5 out of 30 cases (17%). These variants were identified in the following genes BACH2, TLR7, TINF2, NFK2B and MAGT1. Overall mortality was 50% and mean intensive care unit (ICU) stay was 9,26 (1-60) days.
Conclusion: Prevalence of pathogenic variants of IEI among children admitted to the PICU for sepsis was 17%. Our study findings support systematic screening of IEI amongst critically ill children admitted to the PICU for sepsis in order to increase our comprehension of sepsis phenotypes and improve outcomes in this group of critically ill children.

Key words: Sepsis, inborn errors of , whole exome sequencing, pSOFA, children

Résumé

Introduction: Le rôle des erreurs innées d'immunité (IEI) dans la susceptibilité au sepsis n'est pas encore identifié et leur prévalence parmi les enfants admis en réanimation pédiatrique pour sepsis est incertaine. Nous avons évalué la prévalence des IEI dans une cohorte d'enfants admis en réanimation pour sepsis et décrit leurs caractéristiques démographiques, microbiologiques et génétiques.
Méthodes: Une cohorte d'enfants admis pour sepsis a été colligée (Janvier 2021- Mars 2023). Les données démographiques ont été collectées et les tests microbiologiques effectués. Un consentement écrit a été obtenu et un séquençage de l'exome complet (WES) a été réalisé.
Résultats: Trente cas ont été inclus. L'âge moyen était de 46,46 mois (1-180 mois). Des micro-organismes ont été identifiés dans 20 cas (66,66%), avec une étiologie bactérienne dans 8 cas, virale dans 6 cas et fongique dans 2 cas. Le score moyen du Pediatric Sequential Organ Failure Assessment (pSOFA) à l'admission était de 6,46 (2-18). La ventilation mécanique s'est avérée nécessaire dans 18 cas. Les inotropes ont été utilisés dans 17 cas. Des variants pathogènes des IEI ont été identifiées dans 6 sur 30 cas (20%), interessant les gènes suivants: BACH2, TLR7, TINF2, POLA1, NFKB2 et MAGT1. La mortalité globale était de 50% et la durée moyenne du séjour était de 9,26 jours (1-60 jours).
Conclusion: La prévalence des variantes d'IEI parmi les enfants admis pour sepsis était de 20%. Notre étude soutient le dépistage systématique des IEI chez ce groupe afin d'accroître notre compréhension des phénotypes de sepsis et d'en améliorer le pronostic.

Mots clés: Sepsis, erreurs innées de l'immunité, séquençage de l'exome entier, pSOFA, enfants

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Introduction

Pediatric sepsis remains a leading cause of morbidity and mortality worldwide(1). Despite access to vaccination, early antibiotics, and advanced healthcare in high-income countries, nearly half of sepsis-related deaths occur in previously healthy children, suggesting underlying immune deficiencies or dysfunctions. The burden of pediatric sepsis is even greater in low- and middle-income countries (LMIC), although data from these regions are often lacking(2). Researchers in LMIC face numerous barriers, including the absence of cost-effective diagnostic tools.

Inborn errors of immunity (IEI) are a heterogeneous group of disorders characterized by disturbances in the development and/or function of the immune system (3). These disorders lead to increased susceptibility to infectious diseases, autoimmunity, autoinflammatory diseases, allergies, and malignancies(4)((5). However the implication of IEI in sepsis susceptibility and their prevalence among children admitted to the pediatric intensive care unit (PICU) for sepsis in African LMIC remains unclear. Additionally, diagnosing IEI in the PICU using usual immunologic investigations is challenging due to severe alterations in lymphocyte counts, immunoglobulin's levels, and complement production during sepsis with multi organ dysfunction. IEI are genetically driven and result from monogenic mutations that cause loss of expression, loss-of-function, or gain-of-function of the encoded protein(6). Therefore, genetic screening particularly through whole exome sequencing (WES) has emerged as a powerful and cost effective tool to identify mutations in genes implicated in these disorders(7).

We hypothesized that children admitted to the PICU with sepsis due to bacterial, viral or fungal infection have underlying genetic variants involved in IEI. Therefore we decided to screen a cohort of these children for pathological variants of IEI using WES.

Methods

We conducted a prospective observational cohort study enrolling all children admitted to our tertiary care hospital's PICU for sepsis, during the period from January 2021 to March 2023. Sepsis was defined as organ dysfunction associated with bacterial, viral or fungal infection. Clinical signs of infection were documented and microbiological and immunological tests were performed. For genetic analyses, written informed consent was obtained from the parents. Organ dysfunction was assessed using the age adapted "Sequential Sepsis related Organ Failure Assessment" score also known as pediatric SOFA or pSOFA. Screening for pediatric sepsis in the pediatric emergency department and initial treatment bundles are outlined in a written local protocol for recognition and rapid transfer to the PICU (8).

We included all children aged 28 days to 18 years admitted for bacterial, viral, fungal sepsis with a pSOFA score of ≥2. We excluded neonatal sepsis, children with surgical, trauma, and burn-related sepsis. Children with known primary or secondary immunodeficiency were also excluded. Secondary immunodeficiency cases discovered during the study were additionally excluded. Children with nosocomial infections were not included.

Genomic DNA was extracted from peripheral blood samples of the patients following standard protocols. WES was performed on the Illumina Hiseq 2500 with an average coverage of >50x. Reads were aligned to the GRCh38 human reference genome using BWA-MEM v0.7.13. Variants were called with the Unified Genotyper GATK v3.2.2 and annotated with the Variant Effect Predictor (VEP)(9). Candidate variants were filtered for minor allele frequency (MAF) <0.01 in gnomAD and the NHLBI Exome Sequencing Project. Clinvar(10) was used to identify already published variants. The bioinformatics tools SIFT, Polypen were used to predict the impact of the mutation on the protein function for newly reported variants. The Combined Annotation-Dependent Depletion (CADD) bioinformatic predictor was used to predict variant pathogenicity, with a CADD score greater than 20 considered significant. Popviz(11) was used to determine mutation significance cutoff (MSC) with a confidence level of 95%. Pathogenic variants with CADD score greater than MSC were selected.

Results

Cohort description

A cohort of 50 patients was enrolled. Two patients were excluded since immunological tests identified secondary immunodeficiency related to HIV infection. In 11 cases, written consent was not obtained and DNA extraction was not possible in 7 cases. In total, 30 patients were eligible for the study. Demographic and general characteristics of the study participants eligible for WES are presented in Table 1.

Table 1. General characteristics

	All n=30, (% or range)
Age (months)	46,46 (1 – 180)
Male	21 (70%)
Female	9 (30%)
Consanguinity	5 (17%)
ICU mortality	15 (50%)
pSOFA, score	6,46 (2-18)
ICU LOS, days	9,26 (1 – 60)
Inotrope support	17 (57%)
Mechanical ventilation	18 (60%)
Renal replacement therapy	3 (10%)

PICU mortality: pediatric intensive care unit mortality; **pSOFA**: pediatric sequential (sepsis related) organ failure assessment; **PICU LOS**: pediatric intensive care unit length of stay; **n**: number.

Sepsis related data

Sepsis related information including the infection site, the identified pathogen and biological markers are represented as follows. The most common infection

sites in our cohort were pneumonia (37%, 11/30), central nervous system (37%, 11/30) and gastro-intesinal infection (10%, 3/10). The following microorganisms were identified: Streptococcus pneumonia in 2 cases, Staphylococcus aureus in one case, Neisseria meningitidis in 2 cases, Haemophilus influenza in one case, Mycobacterium tuberculosis in 4 cases, Herpes Simplex Virus in 2 cases, SARS-COV2 in 2 cases, Influenza A virus in 1 case, Parainfluenzae virus in one case and Candica albicans in 2 cases. No microorganism was identified in 10 out of 30 cases (33%). The following biological markers were assessed: leucocytes count, lymphocytes count and C-reactive protein. The mean leucocyte count was 14092 E/mm3 (540- 59100), the mean lymphocyte count was 2690 E/mm3 (480 – 8110), the mean platelet count was 281533E/mm3 (10000 – 939000) and the mean CRP level was 153mg/l (7-480).

WES findings

WES identified pathogenic variants of IEI in 17% of cases (5/30). All patients with pathogenic variants were male with a mean age of 7 months. Two pathogenic variants were already reported on Clinvar: NM_001322934.2(NFKB2):c.104-1G>C and NM_001367916.1(MAGT1):c.673-1G>A. The three newly reported variants were identified in the following genes: BACH2, TINF2, and TLR7. These variants are described on table 2.

Table 2. Pathogenic variants of IEI

	P1	P2	P3	P4	P5
Age (months)	1	8	20	1	7
Gender	Male	Male	Male	Male	Male
Consanguinity	No	No	Yes, first degree	Yes, first degree	No
Clinical presentation	Meningo-encephalitis Seizures	Acute kidney injury E.COLI infection	Meningitis Cerebral access	Septic shock Pneumonia Cerebral hemorrhage Neurological disability	SARS-COV2 pneumonia with pleural effusion
Biological and Immunological findings	Lymphopenia Normal C3 C4 and CH50 Normal IgG, IgM Slightly elevated IgA	Anemia Lymphopenia Low CD3, CD4 Normal C3, C4, CH50 Normal immunoglobulins levels	Lymphopenia Normal C3,C4, CH50 Normal IgG, IgA, IgM, Elevated IgE	Neutropenia, Lymphopenia, Low CD3, CD4,CD19, CD16 Normal CD8 Thrombocytopenia Immunoglobulins dosage unavailable Complement dosage unavailable	Anemia, Lymphocytes count normal Normal IgG and IgA Slightly elevated IgM Complement dosage unavailable
Gene	*BACH2*	*TINF2*	*TLR7*	*MAGT1*	*NFKB2*
NM number of the gene	NM_021813.4	NM_001099274.3	NM_016562.4	NM_001367916.1	NM_001322934.2
Protein nomenclature	p.Ser409Pro	p.Tyr154Cys	p.Phe690Ile	NA	NA
Nucleotide nomenclature	c.1225T>C	c.461A>G	c.2068T>A	c.673-1G>A	c.104-1G>C
Status	Heterozygous	Heterozygous	Hemizygous	Heterozygous	Heterozygous
Type	Missense	Missense	Missense	Splice	Splice
SIFT	Tolerated	Deleterious	Deleterious	Already reported on Clinvar as likely pathogenic	Already reported on Clinvar as likely pathogenic
Polyphen	Possibly damaging	Probably damaging	Possibly damaging		
CADD score	23,7	27,6	23,2		
MSC	14,6	20,3	16,3		

Discussion

The prevalence of IEI is increasing exponentially throughout the years (12). The updated classification published in 2022 by the international union of immunological societies reports a total of 485 IEI versus 430 in 2019 and 191 in 2011(13). Nevertheless, more than 50% of children with IEI die before diagnosis and therapy initiation (14). IEI have various and non-specific clinical manifestations and appear at different ages. There is an established link between IEI and susceptibility to infection, however, their implication in pediatric sepsis is unclear and their prevalence amongst children admitted to the PICU for sepsis in North African LMIC is unknown.

In this prospective observational study, we describe for the first time clinical, microbiological, immunological and genetic findings in a cohort of critically ill children admitted to the PICU for sepsis.

We hypothesized that critically ill children (with no comorbidities) admitted to the PICU in the course of an infection have underlying immunodeficiency and/ or immunodysfunction. Therefore, we aimed to assess the prevalence of IEI among these children. While being aware that initial resuscitation leads to modifications in immunoglobulin and complement levels and that lymphopenia/ cytopenia are frequently encountered during sepsis making the interpretation of flow cytometry and lymphocytes subpopulations not conclusive(15), we opted for WES to assess the prevalence of pathogenic variants of IEI.

Five of 30 cases (17%) of pathogenic variants of IEI were

identified. A comparable prevalence was identified in previously published data by Alessadro Borghesi et al. where they assessed prevalence of pathogenic variants of IEI in a cohort of 176 children using WES(16). Variants in IEI genes were identified in 1 out of 5 children(16). Unlike our cohort, which enrolled culture positive and culture negative sepsis, only children with blood culture positive sepsis were included. In another publication describing the prevalence of pathogenic and potentially pathogenic IEI associated variants in a cohort of 330 children, the incidence of IEI variants amongst previously healthy children was estimated at 44% (17). However, the authors state clearly that their study overestimates the prevalence of IEI because they used the QIAGEN's Professional Human Gene Mutation Database (HGMD) database, a resource that in their opinion increases false positives in the assignment of pathogenicity.

In our cohort, IEI's pathogenic variants were identified in the following genes: BACH2, TINF2, TLR7, NFKB2, and MAGT1. We checked for already reported variants on Clinvar. Two variants are already reported and three were not.

The first previously reported variant is NM_001322934.2(NFKB2):c.104-1G>C. NFKB2 plays a major role in B cell development, humoral responses, natural killers and T cells regulation(18). Variants of this gene are associated with common variable immunodeficiency(19). This variant is linked to common variable immunodeficiency -10 (CVID-10). Common CVID10 is an autosomal dominant primary immunodeficiency characterized by childhood-onset of recurrent infections, hypogammaglobulinemia, and decreased numbers of memory and marginal zone B cells. Our patient presented with severe pneumonia with pleural effusion secondary to SARS-COV2 infection. He had normal lymphocytes counts, normal IgG, IgA and slightly elevated IgM. However, lymphocytes subpopulations were not available in this case and immunoglobins results were obtained in the course of the current sepsis episode.

The second previously reported variant is NM_001367916.1(MAGT1):c.673-1G>A. MAGT1 plays an important role in T cell mediated immune reponse and is incriminated in neurological disability(20) which was a phenotypical feature reported in our case. Moreover, this variant is implicated in X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection and neoplasia also known as XMEN. It is an X-linked recessive immunodeficiency characterized by CD4 lymphopenia, severe chronic viral infections, and defective T-lymphocyte activation(21). Neutropenia and hypogammaglobulinemia (IgM, IgG and/or IgA), are also described. Our patient presented with lymphopenia, CD4 lymphopenia and neutropenia in a course of a pulmonary infection. Data about EBV infection was not available in his case.

The three newly reported variants are described here as follows. The first variant is NM_021813.4(BACH2):c.1225T>C. BACH2 is a protein coding gene located on the human chromosome 6 (6q15). The protein contains highly conserved functional domains and controls the terminal differentiation and maturation of both B and T lymphocytes(22). Our variant consisted in an aminoacid substitution of Serine (Ser) which is a polar amino acid, with Proline (Pro), a non-polar amino acid. This substitution can affect the protein's function and hence have impact on the immune system's response in sepsis. Single nucleotide variants in the BACH2 locus have been associated with multiple autoimmune diseases including systemic lupus erythematosus (23). A syndrome of BACH2-related immunodeficiency and autoimmunity (BRIDA) is newly reported in 2017 (24) in relation with BACH2 haploinsufficiency. Described features include immunoglobulin deficiency and colitis. BRIDA is described in adults and no data about its presentation in children is available. Our patient presented with a severe viral meningoencephalitis. Immunological findings included lymphopenia, normal IgG and IgM levels and slightly elevated IgA. The patient's age (1month) in addition to sepsis related immune dysfunction makes interpreting the immunological findings not conclusive.

The second variant NM_001099274.3(TINF2):c.461A>G results in a substitution of tyrosine with cysteine, two amino-acids with different properties, which can alter the protein's stability and impact its critical role in telomere regulation(25). TINF2 mutation have been linked to various syndromes such as dyskeratosis congenita(26), aplastic anemia in children(27) and cancer predisposition syndrome(28). Our patient presented with sepsis associated to sepsis related acute kidney injury in a course of an E.COLI infection and all bioinformatic tools classified this variant as pathogenic. He did not present any clinical features consistent with dyskeratosis congenita, however he presented with anemia and lymphopenia with low CD3 and CD4.

The third variant, NM_016562.4(TLR7):c.2068T>A is a missense mutation, where phenylalanine (Phe) at position 690 is replaced by isoleucine (Ile). TLR7 is a protein coding gene that plays a crucial role in recognizing single-stranded RNA from viruses and initiating an immune response. Variations of this gene have been reported in association with immunodeficiency, inappropriate immune response to viral infections and immune dysregulation. Our patient presented with meningitis complicated by cerebral abscess and recent studies showed that upregulation of TLR7 could potentially induce an inflammatory reaction that aggravate meningitis(29).

While identifying a pathogenic or potentially pathogenic variants related to primary immunodeficiency does not necessarily equate with immunodeficiency and even if well-established pathogenic variants do not always cause a disease, our cohort study establishes a link between variations in immunodeficiency genes and pediatric sepsis. Furthermore, identifying these variants will help clarify the sepsis related immune dysfunction, stratify sepsis phenotypes and potentially guide immunomodulatory therapies.

Limitations and conclusion

Our study has some limitations. It is a cohort study and the sample's size is small. Data on specific micro-organisms

causing sepsis is missing in 10 cases. This finding is due to the lack of standardization of molecular diagnosis using PCR in our low middle income setting. The short duration of hospitalization (death within the first 24h of admission) was a barrier to extensive microbiological and immunological testing in some cases. Additionally, WES is not routinely performed in our setting and is reserved to research studies which limited the number of patients enrolled in this study.

Conclusion

Our study represents the first cohort study describing the prevalence of pathogenic variants of IEI among pediatric sepsis patients admitted to a Moroccan PICU. A 17% prevalence underscores a significant association between genetic variants of IEI and pediatric sepsis. By identifying new pathogenic variants in genes like BACH2, TINF2 and TLR7 we have shed light on potential mechanisms of immune dysfunction in these critically ill children. These findings advocate for systematic screening of IEI among all children admitted to the PICU for sepsis. Implementing such screening protocols could enhance diagnostic accuracy, facilitate timely therapeutic interventions during hospitalization, and guide essential prophylactic measures following ICU discharge.

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