



Hypoparathyroidism-Retardation-Dysmorphism Syndrome due to a Variant in the *Tubulin-Specific Chaperone E* Gene as a Cause of Combined Immune Deficiency

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Abstract

Background Hypoparathyroidism-retardation-dysmorphism (HRD) syndrome is a disease composed of hypoparathyroidism, growth retardation, severe developmental delay, and typical dysmorphic features caused by the tubulin-specific chaperone E gene variant. Many patients succumb in infancy to HRD due to overwhelming infections mainly caused by *Pneumococcus* spp. Knowledge related to the immune system in these patients is scarce.

Purpose To define the immune phenotype of a cohort of HRD patients including their cellular, humoral, and neutrophil functions.

Methods The study included HRD patients followed at Soroka University Medical Center. Clinical and immunological data were obtained, including immunoglobulin concentrations, specific antibody titers, lymphocyte subpopulations, lymphocyte proliferation, and neutrophil functions.

Results Nine patients (5 females and 4 males) were enrolled, aged 6 months to 15 years. All received amoxicillin prophylaxis as part of a routine established previously. Three patients had bacteremia with *Klebsiella*, *Shigella* spp., and *Candida*. Three patients had confirmed coronavirus disease 19 (COVID-19), and two of them died from this infection. All patients had normal blood counts. Patients showed high total IgA and IgE levels, low anti-pneumococcal antibodies in spite of a routine vaccination schedule, and reduced frequency of naive B cells with increased frequency of CD21lowCD27- B cells. All patients had abnormal T-cell population distributions, including reduced terminally differentiated effector memory CD8, inverted CD4/CD8 ratios, and impaired phytohemagglutinin (PHA)-induced lymphocyte proliferation. Neutrophil superoxide production and chemotaxis were normal in all patients tested.

Conclusion HRD is a combined immunodeficiency disease with syndromic features, manifesting in severe invasive bacterial and viral infections.

Keywords Hypoparathyroidism-Retardation-Dysmorphism (HRD) syndrome · Sanjad–Sakati syndrome · Inborn Errors of Immunity (IEI) · combined immune deficiency

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Introduction

Hypoparathyroidism-retardation-dysmorphism (HRD) syndrome, also known as Sanjad–Sakati syndrome [1–3], (OMIM # 241,410), is an autosomal recessive disease composed of hypoparathyroidism, both intra-uterine and post-natal severe growth retardation, severe mental retardation, and dysmorphism.

HRD is caused by variants in the gene encoding tubulin-specific chaperone E (TBCE), which is important for microtubule assembly pathways [3]. The common cause for HRD among the Arab Bedouin population is homozygosity for a founder variant NM_001079515.3:c.155_166del (c.155_166del p.Ser52_Gly55del) [3]. Variants in TBCE, with autosomal recessive traits, were also described as causing Kenny–Caffey syndrome, type 1, KCS1 (OMIM #244,460), which shares very similar features. Other important characteristics of the syndrome are significant delay in achieving developmental milestones, and significantly arrested gross and fine motor skill development. Speech is never achieved by some patients, whereas others have incomprehensible speech [4]. Eye and brain anomalies are common, as are multiple endocrine deficiencies (including hypothyroidism, adrenal insufficiency, and hypogonadism), epilepsy, and bowel obstruction. [5]. Susceptibility to pneumococcal infections is a significant aspect of this syndrome, as many patients succumb in infancy due to these infections. In a recent publication reporting a long-term follow-up of a large cohort of HRD patients, 33 out of 63 patients died before reaching the age of 5 years [4]. All but one patient died from infections, which included septic shock, meningitis, and pneumonia. The introduction of amoxicillin prophylaxis as an institutional practice in 2000 has reduced the mortality rate under 5 years of age from 77 to 24% [4]. The first clinical descriptions of HRD patients by Richardson et al. in 1990 reported normal immunoglobulin levels and a reduced number of T-lymphocyte subsets [1]. Sanjad and Sakati in 1991 reported normal T- and B-lymphocyte counts and mitogen response [2]. A year later, Kalam and Hafeez reported one patient with low IgG and IgA levels, normal B- and T-lymphocyte subsets and CD8/CD4 ratio, and normal thymus in a CT scan [6]. In 2007, Hershkovitz et al. reported hyposplenism, impaired neutrophil chemotaxis, and phagocytosis without significant differences in superoxide production [7]. Autoimmunity was also reported as some patients were described with Hashimoto thyroiditis [5, 8]. In this study, we aimed to describe the immune phenotype of a cohort of HRD patients including cellular, humoral, and neutrophil functions.

Methods

This study included genetically diagnosed HRD patients, who were followed at Soroka University Medical Center in a study conducted during 2021–2022.

Clinical data were obtained from electronic medical records and included demographic, clinical, and laboratory data.

The immunological evaluation was performed during ambulatory clinic visits, while patients were free of infection. All patients received vaccinations as per the mandatory schedule, including diphtheria-tetanus-pertussis, conjugated pneumococcal Prevenar 13, hepatitis B, and Hemophilus influenza type B vaccines. Four patients received Pneumovax vaccine during the last 6 months of the study period. The workup included IgG, IgM, IgA, and IgE levels; specific antibodies (anti-tetanus, pneumococcal, hepatitis B, and diphtheria); lymphocyte subpopulations by flow cytometry; lymphocyte proliferation by PHA; and neutrophil functional tests including superoxide production and chemotaxis. For detailed methods, please see the Supplemental Materials section.

Results

Patient Cohort and Clinical Course Nine patients (5 female and 4 male) were enrolled in the study, with an age range from 6 months to 15 years (mean 6.3 years). Two patients died from COVID-19 infection a few weeks after enrollment (Table 1). All patients were homozygous for the NM_001079515.3:c.155_166del variant. Table 1 outlines the main infection events during the patients' lifetime and other significant clinical features. As part of institutional routine, all patients received amoxicillin prophylaxis, yet suffered from recurrent episodes of otitis media and pneumonia. Two patients (5 and 6, respectively) had bacteremia with *Klebsiella* and *Shigella* spp., and another patient experienced septic shock due to *Candida*. Patients 7 and 8 had urinary tract infections with *E. coli* spp., as did another patient due to *Candida* (Table 1). As for viral infections, seven out of nine patients were tested for COVID-19. Three were positive and two of them died due to acute respiratory distress syndrome (ARDS) associated with the virus. Infections with common viruses such as influenza A, adenovirus, parainfluenza, and RSV virus were severe enough to warrant hospitalization in six patients (Table 1).

In agreement with the known phenotype of the syndrome, all patients exhibited hypoparathyroidism, severe growth retardation, severe progressive developmental delay, and hearing loss. The oldest patient's weight did not exceed 15 kg, and none of the patients was able to communicate verbally. Of note are two patients with additional endocrinopathies—hypothyroidism in one and adrenal insufficiency in the other—who did not survive COVID-19 infection.

Table 1 Clinical features of HRD patient cohort

	P1	P2	P3	P4	P5	P6	P7	P8	P9
Current age (years)	15	10	8	6	6	5	4	2	0.5
Gender	Female	Male	Female	Female	Male	Male	Female	Female	Male
Survival	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Age at death	-	-	-	-	-	5 years	-	-	6 months
Severe bacterial/fungal infections (life time infection)	Septic shock with Candida	Recurrent pneumonia	Influenza A coronavirus (not COVID-19)	Recurrent lobar pneumonia	<i>Shigella flexneri</i> bacteremia	<i>Klebsiella oxytoca</i> bacteremia	<i>E. coli</i> UTI hMPV	<i>E. coli</i> UTI	<i>E. coli</i> UTI
Viral infections	Recurrent lobar pneumonia	Parainfluenza adenovirus	Parainfluenza adenovirus	Parainfluenza adenovirus	RSV influenza A	Candida UTI RSV adenovirus parainfluenza			
COVID-19	No data	Negative	Negative	Negative	Negative	Positive	Positive	No data	Positive
Other	Hypothyroidism epilepsy	Epilepsy	Epilepsy			Adrenal insufficiency			

hMPV, human metapneumovirus; UTI, urinary tract infection; RSV, respiratory syncytial virus

Immunological Workup

Immunoglobulins and Specific Antibodies

High IgG levels were recorded in three out of nine patients, elevated IgA titers in five of nine, and IgE levels were also markedly increased, up to 1000 IU/mL, in four out of six patients tested. All patients were vaccinated according to schedule including diphtheria-tetanus-pertussis (DTP), hepatitis B vaccine, and conjugated anti-pneumococcal vaccine (Prevenar 13). Four of the older patients received Pneumovax vaccine. All patients had low total anti-pneumococcal antibodies in spite of serial Prevenar 13 vaccination and recurrent ear and pulmonary infections. Only one patient had a post-Pneumovax vaccine antibody titer. Two patients had low, non-protective anti-tetanus antibody titers, and two had only short-term protective levels (Table 2).

Lymphocyte Phenotyping and Proliferation Studies

Both T- and B-cell population distributions were abnormally skewed in most patients. In seven patients, an inverted CD4/CD8 ratio was recorded, attributed to CD8 expansion, as none of our patients had CD4 lymphopenia (Table 2). In six patients, a detailed T- and B-subpopulation analysis was performed. A reduced frequency of naive B cells and increased percentage of plasmablast B cells were found in four patients. An increased frequency of CD21^{low}CD27⁻ B cells was evident in all patients. As for T-cell populations, three out of six patients had a low percentage of CD4 effector memory and of terminally differentiated subsets that expressed CD45RA (TEMRA). There was notable CD8 lymphocytosis with an increased percentage of central memory cells, a low percentage of effector memory, and a prominent reduction in TEMRA cells in all tested patients (Table 3). Lymphocyte proliferation tests by mitogen stimulation with PHA were poor—at or below 50% of controls in four out of the nine of patients tested (Table 2). Neutrophil functions, as tested by superoxide production and chemotaxis, were normal in all patients tested (Table 4). Of note are the results from the severe combined immunodeficiency (SCID) newborn screening program using a T-cell receptor excision circle (TREC) assay that was introduced in 2015. Three patients enrolled in this study were born after 2015, and all had normal TREC results.

Discussion

Our study establishes HRD syndrome, due to the previously described Arab founder variant in the TBCE gene, as an inborn error of immunity that should be classified as

Table 2 Immunoglobulins, specific antibodies, lymphocyte populations, and proliferation studies

	P1	P2	P3	P4	P5	P6	P7	P8	P9	Reference range
Age (years)	15	10	8	6	6	5	4	2	0.5	
Immunoglobulins	1900 ↑	1880 ↑	1400	1500 ↑	430	850	1000	1040	240	Reference range [^]
IgG (mg/dL)	440 ↑	550 ↑	420 ↑	330 ↑	820 ↑	160	170	200	40	(Mayo clinic laboratory reference)
IgA (mg/dL)	80	50	70	60	37	51	50	65	13 ↓	
IgM (mg/dL)	1000 ↑	ND	410 ↑	170	450 ↑	780 ↑	ND	25	ND	
IgE (U/mL)	0.54	0.68	0.72	0.17	0.22	0.03	0.03	0.49	ND	See below
Specific antibodies (IU/mL)	0.2	1.5	1.5	0.5	1.8	1.5	2.1	1.5	ND	> 0.5 ^A , > 0.1 ^B
Tetanus toxoid (mg %)	ND	6.5	ND	ND	40	ND	25	ND	ND	2–9999
Hepatitis B (mIU/mL)	ND	0.089	ND	ND	0.043	0.02	0.071	ND	ND	10
Diphtheria (IU/mL)	58%	65%	94%	37%	100%	92%	100%	48%	41%	0.01–0.1
PHA responses (stimulation index % of control)	2.02 (1–2.2)	3.12 (1.2–2.6)	2.23 (1.2–2.6)	3.7 (1.2–2.6)	4.03 (1.2–2.6)	3.2 (1.2–2.6)	2.17 (1.4–2.6)	2.96 (1.4–6.2)	2.56 (1.9–5.9)	normal > 50% of control
Lymphocyte subpopulations	0.64 (0.5–1.3)	0.94 (0.6–1.5)	1.31 (0.6–1.5)	1.2 (0.6–1.5)	0.98 (0.6–1.5)	0.84 (0.6–1.5)	0.93 (0.7–3.4)	1.38 (0.7–3.4)	1.6 (1.4–4.3)	
CD3 (× 10 ³ cells/μL)	1.4 (0.3–0.9) ↑	2.08 (0.4–1.1) ↑	0.85 (0.4–1.1) ↑	2.25 (0.4–1.1) ↑	3.05 (0.4–1.1) ↑	2.3 (0.4–1.1) ↑	1.16 (0.5–2)	1.5 (0.5–2)	0.93 (0.5–1.7)	
CD4 (× 10 ³ cells/μL)	0.26 (0.1–0.6)	0.25 (0.27–0.8)	0.83 (0.27–0.8)	0.78 (0.27–0.8)	1.2 (0.27–0.8)	0.5 (27–0.8)	0.64 (0.4–2.6)	0.92 (0.4–2.6)	1.56 (0.3–3)	
CD8 (× 10 ³ cells/μL)	0.05 (0.07–0.5)	0.16 (0.1–0.5)	0.13 (0.1–0.5)	0.15 (0.1–0.5)	0.07 (0.1–0.5)	0.93 (0.1–0.5)	0.23 (0.13–0.9)	0.39 (0.13–0.9)	0.6 (0.16–1.1)	
CD19 (× 10 ³ cells/μL)	0.9%	ND	4.5%	ND	ND	ND	ND	2.6%	4%	
CD56/CD16 (× 10 ³ cells/μL)										
γδ T cells (% of CD3 +)										

ND, not done; ^A > 0.5, short-term protection; ^B > 1.0, long-term protection; PHA, phytohemagglutinin; ↓, low; ↑, high

[^]Clinical laboratory reference: IgG 5–8 months, 164–588 mg/dL; 2–3 years, 295–1156 mg/dL; 4–6 years, 386–1470 mg/dL; 7–9, 462–1682 mg/dL; 10–12 years, 503–1719 mg/dL; 13–15 years, 509–1580 mg/dL. IgA 5–<9 months, 16–50 mg/dL; 2–<4 years, 27,246 mg/dL; 4–<7 years, 29–256 mg/dL; 7–<10 years, 34–274 mg/dL; 10–<13 years, 42–295 mg/dL; 13–<16 years, 52–319 mg/dL; IgM 5–<9 months, 32–132 mg/dL; 2–<4 years, 37–184 mg/dL; 4–<7 years, 37–224 mg/dL; 7–<10 years, 38–251 mg/dL; 10–<13 years, 41–255 mg/dL; 13–<16 years, 45–244 mg/dL. IgE 6–11 months < or = 34; 1 and 2 years < or = 97; 4–6 years < or = 307; 7 and 8 years < or = 403; 9–12 years < or = 696; 13–15 years < or = 629

Table 3 T- and B-cell subpopulations

	P1	P3	P4	P5	P8	P9
CD4+ T-cell populations*						
Naïve CD197+/45RA+/27+++/57-	32% (37-97)	70% (46-99)	50% (46-99)	48% (46-99)	77.5% (52-92)	75% (66-100)
Central-memory CD197+/45RA-/27+/57-	55% (13-76)	26% (13-76)	40% (13-76)	38% (13-76)	21% (0.09-40)	22% (4-41)
Effector-memory CD197-/45RA-/27+/57+	0.3% (0.49-25)↓	0.1% (0.27-18)↓	2.5% (0.27-18)	5% (0.27-18)	0.3% (0.024-4.7)	0 (0.0025-1)↓
TEMRA CD197-/45RA+/27-57++	0 (0.004-5)↓	0.02% (0.003-1.8)↓	1.5% (0.003-1.8)	1.5% (0.003-1.8)	0.04% (0.003-4.1)	0 (0.005-0.05)↓
CD8+ T-cell populations*						
Naïve CD197+/45RA+/27+++/57-	32% (20-95)	83% (16-100)	28% (16-100)	7.5% (16-100)↓	66% (10-100)	58% (44-100)
Central-memory CD197+/45RA-/27+/57-	22% (0.4-18)↑	14% (1-6)↑	20% (1-6)↑	10% (1-6)↑	10% (1-8)↑	37% (2-35)↑
Effector-memory CD197-/45RA-/27+ -/57+	0.8% (4-100)↓	1% (5-100)↓	20% (5-100)	60% (5-100)	13% (2-100)	0.1% (1-23)↓
TEMRA CD197-/45RA+/27+ -/57++	0.5% (9-65)↓	0.4% (15-41)↓	15% (15-41)↓	6% (15-41)↓	4% (8-71)↓	0 (3-42)↓
B-cell population^						
Naïve B cells	35% (61-87)↓	39% (58-64)↓	69% (59-88)	63% (59-88)	64% (69-90)↓	73% (93-97)↓
Non-switched memory	5% (2.6-13.4)	12.4% (3.1-18)	4.1% (3.1-18)	3.1 (3.1-18)	5% (4.6-16.3)	70.9% (0.8-4.7)
Double-negative CD20 ⁺ CD27 ⁺	25% (2.6-13)↓	13.6% (3-21)	7% (3-18)	4% (3-18)	10.5% (4.6-16)	24% (0.8-4.7)↑
CD20 ⁺ /CD27 ⁺ /IgM ⁻ /IgD ⁻ CD2 ^{-low} switched	29% (4-21)↑	13.8% (4.4-20)	11% (2.9-17)	7% (2.9-17)	5.5% (2.7-12.5)	0.5% (0.1-1.0)
CD21 ^{low} /cd27 ⁻	23% (0.9-3)↑	13% (0.9-3.5)↑	14.6% (0.9-3.5)↑	12% (0.9-3.5)↑	7% (1.8-3.6)↑	12% (0.3-4)↑
Plasmablasts	4% (0.3-1.3)↑	11.6% (0.7-3.5)↑	2.6% (0.7-3.5)↑	1.3% (0.7-3.5)	3% (0.6-2.3)↑	0.2 (0.2-1)

* T-cell differentiation presented as % of CD4 or CD8 cell population, ^ B-cell differentiation presented as % of CD19+ ↓, low; ↑, high

Table 4 Neutrophil chemotaxis and superoxide production

Patient	P1	P2	P3	P4	P5	P6	P7	P8	P9	Reference range
Superoxide production										
Resting	3	3	9	3	5	3	8	5	7	1–6 nmol O ₂ /10 ⁶ cells/min
FMLP	54	38	34	27	18	ND	73	ND	ND	13–42 nmol O ₂ /10 ⁶ cells/min
OZ	56	38	38	22	19	ND	51	ND	ND	11–38 nmol O ₂ /10 ⁶ cells/min
PMA	60	43	62	46	35	38	40	54	58	12–46 nmol O ₂ /10 ⁶ cells/min
Chemotaxis										
FMLP	30 (71%)	42 (100%)	40 (95%)	19 (44%)	26 (CM)	42 (93%)	42 (100%)	33 (80%)	33 (83%)	35–45 (%control)
Random migration	19 (68%)	24 (114%)	27 (96%)	13 (43%)	20 (CM)	21 (88%)	23 (110%)	21 (75%)	18 (82%)	20–30 (%control)
Chemotaxis A-B	1.6	1.8	1.5	1.5	1.3	2.0	1.8	1.6	1.8	Ratio control/patient

FMLP, formyl-methionyl-leucyl-phenylalanine; ND, not done; OZ, opsonized zymosan; PMA, phorbol myristate acetate

a combined immunodeficiency (CID) disease with syndromic features. Patients frequently display impaired mitogen responses, T cell-dependent antibody responses, and reduced frequencies of CD4+ and CD8+ effector memory of CD4+ and CD8+ TEMRA and naive B cells, with an increased proportion of CD21lowCD27- B-cell populations. They suffer from varied bacterial infections in spite of amoxicillin prophylaxis and display opportunistic viral and fungal infections.

Historically, these patients had a high mortality rate due to pneumococcal infections, but this was reduced significantly upon introduction of amoxicillin prophylaxis (4). Although patients continued to die due to severe sinopulmonary infections, these invasive pneumococcal infections were significantly lower in patients adhering to this regimen. TBCE is important for assembly pathways of microtubules, and hypoparathyroidism causes impaired calcium homeostasis. Thus, HRD syndrome encompasses two features that can influence normal activity of the immune system.

Microtubules are essential for immunological synapse (IS) formation of both T and B lymphocytes [9, 10], exocytosis of cytotoxic granules, secretion of chemokines from T cells [11], and antigen-dependent CD8 T-cell activation [12]. Our findings are in line with other known CIDs with cytoskeleton abnormalities such as Wiskott–Aldrich syndrome (WAS) and dedicator of cytokinesis 8 (DOCK8). As shown in the presented study, HRD patients share some phenotypic features with those disorders, including elevated IgA and IgE concentrations and abnormal humoral response. All HRD patients are afflicted with hypoparathyroidism, and are thus treated with calcium supplements and active vitamin D metabolites. Hypocalcemia is the most prevalent complication seen among our patients, starting a few hours after birth, and both hypo- and hypercalcemia are common complications, reflecting treatment difficulties. Regulated changes in calcium concentrations in lymphocytes control the complex pathways of proliferation, differentiation, antibody and cytokine secretion, and cytotoxicity, and diseases such as Ca⁺² release-activated Ca⁺² (CRAC) channelopathy (ORAI1, STIM1, etc.) can cause immunodeficiency [13–17]. At present, there are no data to support such a mechanism in HRD patients, and we believe this to be worth future study.

An interesting finding found in all six patients with a detailed analysis of lymphocyte subpopulations was an increase in CD21lowCD27- B cells. The frequency of these cells is often increased in immunodeficiency patients, such as in common variable immune deficiency (CVID) and in those with autoimmunity disorders [18]. These cells have been described as anergic naive B cells to resemble exhausted memory B cells [19]. This finding, although non-specific, may further point to the fundamental immunological abnormalities in HRD patients.

Two of the patients who tested positive for COVID-19 died during the research period. This, at least in part, could be attributed to the apparent combined immunodeficiency involving both T- and B-cell defects, in combination with other features. It is of importance to note that both patients were on the severe spectrum of the syndrome, with extremely restricted growth and developmental delays, and one of these patients had adrenal insufficiency, which may serve as a significant risk factor for mortality. As far as other possible mechanisms, abnormal type I interferon responses serve as a risk factor for higher morbidity and mortality from COVID-19. [20] Assembly pathways of microtubules, as well as calcium signaling impairment, have also been reported to affect interferon response [21]. However, the very small number of patients affected, as well as those willing to be vaccinated, mandates further follow-up, data collection, and study before any conclusions can be drawn in regard to this intriguing issue.

The limitations of this study are reflected in the inclusion of patients with a single variant and the relatively small sample size. Since it is possible that other HRD patients may have similar or different immune abnormalities, further research with HRD patients who are homozygous for other TBCE variants is required.

As far as treatment options for CID, hematopoietic stem cell transplantation (HSCT), currently the definitive and most rewarding option, is less likely to be beneficial to our patients. The severe physical and mental developmental delays, as well as hypoparathyroidism, are the most pronounced aspects of this severe syndromic inborn error of immunity (IEI), which cannot be corrected by HSCT and will probably not contribute to either patient life quality or longevity. However, considering our current results, it is worthwhile to compare the added benefit of IVIg treatment in some of these patients to the current antibiotic prophylactic regimen as part of their routine treatment.

Conclusion

In this study, we demonstrated that HRD patients should be classified as IEI group of CID with syndromic features, manifesting in varying degrees of severity. This should alert physicians and mandate an in-depth investigation and careful follow-up for each patient, with administration of appropriate prophylaxis regimens.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10875-022-01380-9>.

Author Contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Odeya David, Eyal Kristal, and Amit Nahum. Flow cytometric analysis, proliferation studies, and neutrophil functional tests

were performed by Nurit Hadad and George Shubinsky. The manuscript was written by Odeya David, Eyal Kristal, Arnon Broides, and Amit Nahum. All authors have read and approved the final manuscript. Odeya David and Eyal Kristal are co-authors.

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Data Availability The datasets generated during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics Approval The study was approved by the Soroka University Medical Center Ethics Committee.

Consent to Participate Informed consent was signed by the patients' parents prior to enrollment.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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