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Analysis of clinical and immunologic phenotype in a large cohort of children and adults with cartilage-hair hypoplasia

To the Editor:

Cartilage-hair hypoplasia (CHH) is a chondrodysplasia with variable immunodeficiency. Patients' immunologic and clinical phenotypes are highly variable and correlate weakly. Most previous studies have involved only children, and the quality of immune function in adults with CHH remains largely unknown. In addition, paucity of data exists regarding T- and B-cell subpopulations and specific antibody responses in CHH. Here, we report on the clinical and immunologic phenotype in a large group of Finnish children and adults with CHH.

We invited all 110 living Finnish patients with genetically confirmed CHH. Fifty-six individuals (19 males, 37 females; median age, 34 years; range, 0.7-68 years) agreed to participate, with informed consent. The study protocol was approved by the Institutional Research Ethics Committee. Clinical data were collected, and laboratory tests performed (see the Methods section in this article's Online Repository at www.jacionline.org). Correlations between laboratory parameters and clinical manifestations were analyzed with the Fisher exact test, the Mann-Whitney test or the Kruskall-Wallis test, and regression analysis, as appropriate.

All patients were homozygous (n = 43) or compound heterozygous (n = 13) for the *RMRP* g.70A>G mutation. Table I describes clinical features. We grouped patients as having (1) no symptoms/signs of immunodeficiency (n = 15 [27%]), (2) features of humoral immunodeficiency only (n = 26 [46%]), and (3) features of combined immunodeficiency (CID, n = 15 [27%]) (see Table I for definitions).

Laboratory findings are presented in Fig 1 and Tables E1 and E2 in this article's Online Repository at www.jacionline.org. Common pattern of abnormalities in the B- and T-cell subpopulations (see Table E2) included (1) decreased $CD3^+CD4^+CD45RA^+CD31^+$ recent thymic emigrants (RTEs), naive $CD4^+$ cells, and naive $CD8^+$ cells; (2) increased activated $CD4^+$, central memory $CD4^+$, and effector memory $CD8^+$ cells; (3) normal $CD4^+CD25^{high}CD127^{low}$ regulatory T cells; (4) decreased naive, transitional, and $CD19^+CD27^+$ memory B cells; and (5) increased activated $CD21^{low}CD38^{low}CD19^+$ cells. The reduced counts of rapidly proliferating cells (naive B, T, and RTE) support a disturbed cell cycle as an important pathogenic mechanism.[1] The pattern of abnormalities in B-cell subpopulations indicate B-cell production and germinal center defect, while decreased $CD27^+$ B cells suggest defective maturation or survival.[2]

Preexisting tetanus toxoid antibody levels were below 0.1 IU/mL in only 3 of 43 patients (Table E1). Seven out of 8 (88%) patients who agreed to receive Pneumovax vaccine demonstrated specific antibody deficiency (SAD) (see Table E3 in this article's Online Repository at www.jacionline.org). Clinical features of the 7 subjects with SAD included rhinosinusitis (n = 6), otitis media (n = 5), warts (n = 3), malignancies (n = 3; lymphoma, basal cell carcinoma, uterus carcinoma), severe varicella requiring hospitalization (n = 2), and recurrent herpes simplex virus infection (n = 1). Patients with SAD showed clinical signs of humoral (n = 2) and combined (n = 4) immunodeficiency. SAD may therefore be a marker of more severe disease and vaccine responses should be routinely studied after infancy.

Patients with no clinical signs of immunodeficiency showed no specific pattern of laboratory abnormalities. No correlation was observed between history of pneumonia or rhinosinusitis and immunologic defects. Genotype did not correlate with any clinical or laboratory parameter.

Patients with clinically suggested CID showed decreased median $CD3^+$, $CD8^+$, and RTE counts (see Table E4 in this article's Online Repository at www.jacionline.org). Of these parameters, RTE counts demonstrated the strongest trend toward significance in multiple regression analysis ($P = .094$, B coefficient, -15.628). Lymphocyte proliferative responses were not measured because previous studies have reported that they are abnormal in most patients and show no correlation with clinical manifestations in CHH.[1]

Lower median IgG_2 concentrations (1.08 vs 1.96 g/L; $P = .016$) were observed in patients who required hospitalization for varicella-zoster virus infection. Four out of 5 hospitalized patients (80%) were IgG_2 deficient (IgG_2 range, 0.55-1.47 g/L) compared with 9 out of 37 (24%) nonhospitalized patients ($P = .011$). In multiple regression analysis, only low IgG_2 showed a trend toward significance ($P = .055$, B coefficient, -1.734). The association between IgG_2 deficiency and severe varicella has been described previously,[3] suggesting that patients with CHH with low IgG_2 should be regarded at risk for severe varicella-zoster virus infection. However, these findings require validation in further studies because low IgG_2 may only represent a marker of a more profound immunodeficiency.

We then analyzed laboratory results in various age groups: children younger than 18 years (n = 15), young adults aged 18 to 44 years (n = 23), and adults older than 45 years (n = 18) (see Table E4). Patients older than 45 years demonstrated higher neutrophil and $CD4^+$ cell counts, as well as higher median IgA, IgG, and IgG_2 levels than younger patients. In addition, children showed higher $CD19^+$ cell counts and lower median concentrations of antibodies to tetanus toxoid than adult patients. Although lower immunoglobulin and vaccine antibody levels in pediatric patients may reflect slow maturation of immune system, lower $CD19^+$ and higher $CD4^+$ cell numbers in adults with CHH deserve further studies. Because mortality due to infections and malignancies is increased in CHH,[4] patients surviving into adulthood represent individuals with milder disease. Furthermore, although some *RMRP* gene mutations induce a more severe immunodeficiency,[5] the

TABLE I. Clinical features of the 56 patients with CHH

Clinical feature	Proportion of patients	Comments
Clinical humoral immunodeficiency	26 of 56 (46%)	Defined as otitis media and/or rhinosinusitis requiring surgical interventions, sepsis, pneumonia, and/or bronchiectasis
Clinical combined immunodeficiency	15 of 56 (27%)	Defined as a history of severe warts, recurrent and/or severe herpes virus infections, malignancy and/or autoimmunity, with clinical signs of humoral immunodeficiency
Pneumonia	11 of 56 (20%)	
Recurrent	4 of 11 (36%)	
Requiring hospitalization	5 of 11 (45%)	
Bronchiectasis	10 of 34 (29%)	Diagnosed on lung high-resolution computed tomography
Rhinosinusitis	33 of 56 (59%)	
Sinus surgery	21 of 33 (64%)	
Otitis media	41 of 56 (73%)	
Tympanostomy	16 of 41 (39%)	
Sepsis	3 of 56 (5%)	
History of warts	19 of 56 (34%)	Out of 2 patients with severe warts, one underwent partial amputation of the toe with warts for suspected malignancy and another had protracted history of widespread warts
Warts at the time of visit	14 of 19 (74%)	
Severe warts	2 of 19 (11%)	
Varicella	42 of 56 (75%)	History of varicella and/or positive serology for varicella-zoster virus
Requiring hospitalization	5 of 42 (12%)	
Boils	3 of 56 (5%)	
Recurrent	2 of 3 (67%)	
Mucocutaneous herpes simplex virus infection	2 of 56 (4%)	One patient had required continuous acyclovir prophylaxis for 15 y for recurrent skin herpes simplex virus infections
Allergy	23 of 56 (41%)	History of allergic rhinoconjunctivitis
Malignancy	9 of 56 (16%)	Other malignancies included uterus carcinoma in one patient and vocal cord carcinoma in another
Lymphoma	2 of 9 (22%)	
Basal cell carcinoma only	5 of 9 (56%)	
Other	2 of 9 (22%)	
Autoimmunity	1 of 56 (2%)	Juvenile idiopathic arthritis
Prophylactic antibiotics	7 of 56 (13%)	Sulfamethoxazole/trimethoprim or azithromycin, commenced for recurrent infections or lymphopenia
Immunoglobulin substitution	7 of 56 (13%)	In 4 patients treatment was still ongoing at the time of the study

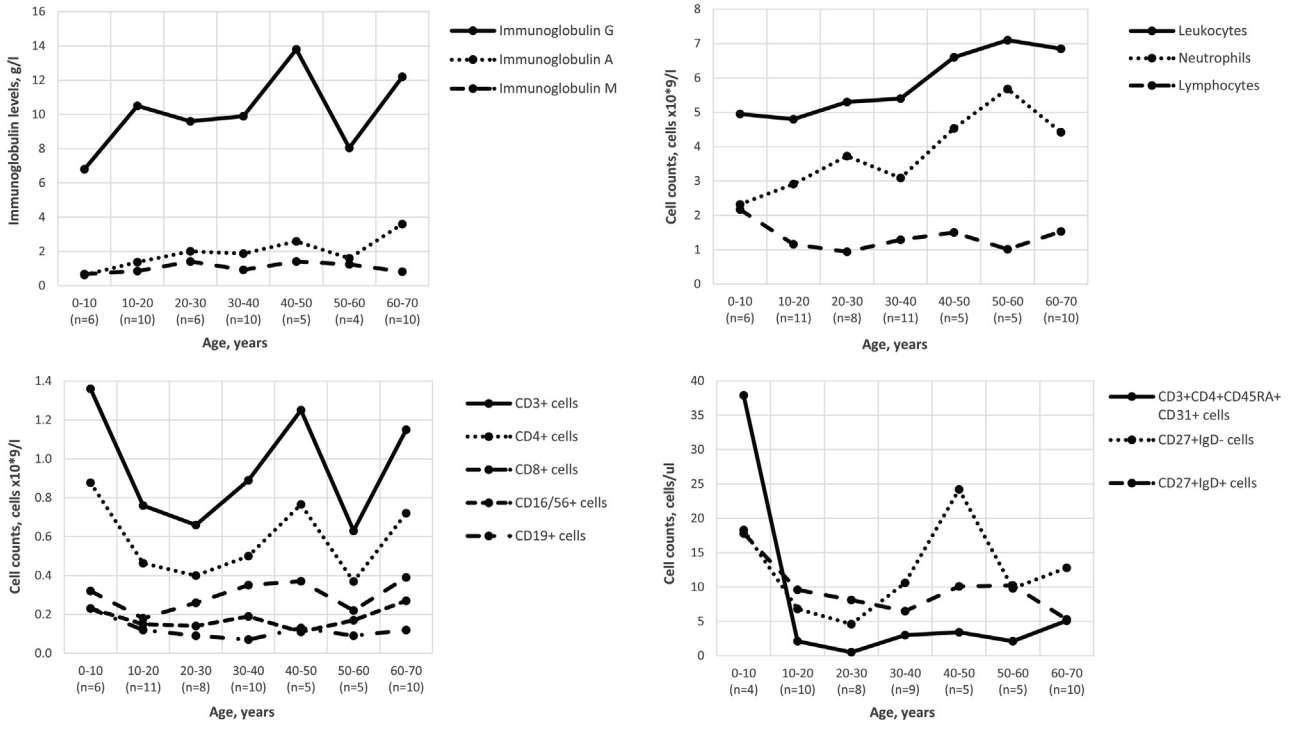

FIG 1. Selected immunologic features in 56 patients with CHH. All laboratory values are shown as medians. Patients are grouped by age and the number of subjects is shown in each age group.