A predominance of g.70A>G mutation in Finnish patients can result in milder presentations.

Consistent with previous reports, measured laboratory values correlated poorly with any assessed symptoms and despite clearly abnormal laboratory indices, few patients developed serious complications. Worldwide, of the 30 subjects with CHH and hematopoietic stem cell transplantation (HSCT) whose genotype has been reported, only 6 patients were homozygous for g.70A>G mutation. Only 1 Finnish child with CHH, homozygote for g.70A>G mutation, has required HSCT for severe hypoplastic anemia, not for immunodeficiency. Thus, selection of patients who would benefit from HSCT based on routinely available laboratory parameters is highly cumbersome in a cohort carrying predominantly RMRP g.70A>G mutations.

The major limitation of this study is the retrospective nature of clinical data. Inclusion of only living patients left out those with CHH who had died of cancer or severe infections. Another limitation is the use of a single laboratory measurement per patient. Results of immunologic tests fluctuate over time and predicting any clinical course on the basis of cross-sectional laboratory values remains challenging.

The observed high number of asymptomatic patients and individuals with clinical signs of humoral immunodeficiency only should be interpreted with caution because clinical features may occur and cumulate with time. Follow-up studies should assess the applicability of clinical and immunological phenotype correlations, including the potential to predict a more severe course (CID) in patients with lower CD3+, CD8+, and RTE counts.

In summary, we demonstrated that approximately one-fourth of the surviving Finnish patients with CHH included in this study manifested clinical signs of CID, while another one-fourth showed no signs of immunodeficiency despite laboratory immunologic abnormalities. This is the first report describing high prevalence of SAD and a specific pattern of abnormalities in B- and T-cell compartments in patients with CHH.

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REFERENCES

We involved 976 practitioners who were required to include the next 4 consecutive patients older than 18 years driving a vehicle and consulting for untreated AR or AR poorly controlled with a previous treatment.

The consequences of AR on daytime awareness were assessed by the EPWORTH drowsiness score and awareness at the wheel by the Karolinska Sleepiness Scale (KSS) score. The EPWORTH scale is made up of 8 questions scored from 0 to 3, giving a sum of 0 to 24, which reflects the severity of daytime drowsiness. The KSS scale is made up of 9 awareness/asleep graduation scales varying from 1 (“extremely awake”) to 9 (“very sleepy, considerable effort needed to remain awake and stop going to sleep”). An ascending hierarchical cluster analysis (Ward method) was used to identify the existence of groups at high risk of drowsiness and driving accidents incorporating the EPWORTH and KSS scores.

In our study, 3850 patients, average age 39 ± 14 years, with a sex ratio close to 1, were included.

In 25.4%, the AR was intermittent and mild; in 8.8%, persistent and mild; in 17.9%, intermittent and moderate to severe; and in 48.0%, persistent and moderate to severe. Half of the patients (53.3%) had a family history of allergy and 84.8% had a personal history of not only AR but also asthma (23.6%) and/or atopic dermatitis (18.2%). Allergy had been confirmed by tests in 46.9% (95% CI, 43.8-49.9) of the patients at risk of reduced awareness and driving accidents, characterized by a peak at severe AR (76.7% vs 54.8%; P < .0001). The group at risk of drowsiness and accident (cluster 1) not only had more severe nasal symptoms than the other patients but also had eye, pharyngeal, and respiratory signs, fatigue, and headaches, which were 1.5 to 2 times as common. As a consequence of their more severe nasal symptoms and more frequent ocular symptoms, they were also more often treated with oral and ocular H1 antihistamine. One limitation of the study is that the type of antihistamines, and especially the proportion of first-generation sedating antihistamines, was not reported.

These results show the impact of AR on the risk of sleeping while driving. Drowsiness is responsible for 1 out of 5 cases of road accidents. It affects all drivers, although some conditions increase the risk. The case of sleep apnea syndrome is well known: when untreated, it triples the accident rate compared with the general population. This risk is not known today for AR but the fact that almost 50% of the patients with AR were at increased risk of a driving accident confers a level of seriousness that is usually not acknowledged. A case control study should be conducted to evaluate the ratio of incidence rate of motor vehicle crashes in patients with AR by comparison to a nonrhinitis population of drivers. This study should also more precisely document the allergic origin of the rhinitis, which is also a limitation of our study. However, the present results, describing an increase in the driving problems described by the patients themselves, justify active management and increased patient information about the risks they run if they are not appropriately treated and adhere correctly to their treatment. They confirm the experimental work of Vuurman et al on a small number of patients who conclude that untreated AR can impair driving ability and put patients at risk and that drug therapy could reduce this impairment. In particular, it is recommended to adapt treatment according to the severity and level of management of the AR and not using sedatives, particularly first-generation H1 antihistamines, which affect driving. Information strategies should also be developed for dispensing pharmacists who are increasingly being consulted directly by patients because of the apparently mild nature of the disorder.

Our study points out the extent of the consequences of AR on daytime drowsiness and awareness when driving and identifies the existence of a homogeneous group of patients at high risk of reduced awareness and driving accidents, characterized by a profile involving severe nasal, ocular, pharyngeal, and respiratory symptoms. These patients should be informed of this risk and managed specifically.

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REFERENCES

Absence of functional fetal regulatory T cells in humans causes in utero organ-specific autoimmunity

To the Editor:

Fetal T regulatory (Treg) cells are present by 13 weeks gestation, but their role during the fetal period is unclear. Maternal Treg cells clearly are critical for fetal tolerance. Human fetal Treg cells promote tolerance to noninherited maternal antigens in utero, but whether tissue-specific self-tolerance is needed in utero is unknown. During pregnancy, fetuses with the genetic disorder Immune dysregulation Polyendocrinopathy Enteropathy X-linked (IPEX) syndrome lack functional Treg cells, but maternal Treg cells remain functional. Patients with IPEX syndrome often appear healthy at birth, but develop early systemic autoimmunity including early-onset diabetes, enteropathy, thyroiditis, and dermatitis. Timing of the initial organ-specific inflammation remains unclear. Early fetal or perinatal IPEX presentations are reported, but evidence for in utero organ-specific autoimmunity is lacking. In this study, we report 2 patients with IPEX syndrome who died shortly after birth with histological evidence for tertiary lymphoid structures, chronic inflammatory changes, and targeted exocrine pancreas autoimmunity in the absence of clinical diabetes. Repertoire analysis demonstrated clonal enrichment within the pancreas consistent with an antigen-driven germinal center reaction. A murine model with inducible inactivation of Treg cells demonstrated similar exocrine-dominant lymphocytic infiltrates in the pancreas. Thus, absence of functional Treg cells promotes organ-specific, exocrine pancreas autoimmunity in utero.

Patient 1 was prenatally diagnosed with IPEX syndrome secondary to a family history of a known pathogenic missense mutation in FOXP3 (c.1087A>G, p.I363V) (see Fig E1 in this article’s Online Repository at www.jacionline.org). Maternal polyhydramnios developed in the absence of fetal hydrops or growth restriction. Prenatal ultrasound detected hyperchoic skin, but was otherwise reassuring. Labor was induced at 39 weeks and immediately the infant developed unexpected respiratory failure requiring intubation. Blood glucose level was normal (57 mg/dL). Hematocrit was 43%, platelets 194,000/μL, and WBCs 10.24 thousand/μL, with only 1% immature granulocytes. Despite oscillatory ventilation, the child lived only 29 hours and died from respiratory failure. Blood cultures and viral infectious screening were negative and placental pathology was normal. A complete autopsy was performed and revealed severe pulmonary hypoplasia as the etiology for respiratory failure. Treg-cell phenotyping performed on cord blood confirmed a lack of CD4+ FOXP3+ CD25hi T cells. Histologic examination revealed prominent lymphocytic infiltrates in the pancreas, gastric mucosa, and thyroid glands but a lack of inflammation in the testes and adrenal and pituitary glands, a pattern typical for IPEX syndrome (see Fig E2 in this article’s Online Repository at www.jacionline.org). The pancreas infiltrate showed tertiary lymphoid-like structures with extensive T-cell (CD3+) zones, including mixed CD4+ and CD8+ cells, surrounding distinct B-cell (CD20+) aggregates (Fig 1). Chronic inflammatory changes were present including squamous ductal metaplasia, acinar atrophy, and stromal fibrosis. We screened inflamed pancreas sections using interphase fluorescence in situ hybridization for X and Y chromosomes (200 cells analyzed) and found an exclusively male (XY) karyotype with no maternal (XX) cells. The histologic findings indicate chronic in utero inflammation, rarely described in fetal tissues.

An additional neonatal IPEX autopsy case, patient 2, revealed similar findings. Patient 2 was the proband with several family cases (FOXp3 c.1189C>T, p.R397W) (see Fig E1). He died at day 19 from peritonitis. Pancreas histology also showed a lymphocyte-rich mononuclear infiltrate within the pancreas, but with more advanced fibrosis (Fig 1). Focal clusters of CD20+ B cells were surrounded by dense CD3+ T-cell zones, with mixed CD4+ and CD8+ staining, as seen in patient 1. In contrast to the 2 patients with IPEX syndrome, control neonatal pancreas tissue obtained from age-matched autopsy cases (n = 5) showed no lymphocytic infiltrates regardless of the cause of death (Fig 1). RNA-seq analysis from patient 1 pancreas tissue showed increased expression of CCL19, CCL21, CCL22, and LTB (lymphotoxin beta) transcripts known to be involved in tertiary lymphoid organization and type 1 diabetes, and interferon-driven proinflammatory chemokines (CXCL9, CXCL10, CXCL11) known to recruit CXCR3+ activated T cells (see Fig E3 in this article’s Online Repository at www.jacionline.org). Overall, the chronic and organized nature of the pancreatic inflammation in both subjects with IPEX syndrome suggests a role for Treg cells in restraining self-reactive T-cell responsiveness before microbial colonization.

Interestingly, islets were structurally intact and there were no significant inflammatory infiltrates in or directly surrounding islets despite the presence of extensive inflammation within surrounding exocrine tissue (Fig 1, columns 1-2). Indeed, there was preferential loss of exocrine tissue compared with age-matched control tissue. Quantitative measurement of insulin-staining islet tissue in both patients with IPEX syndrome revealed sparing of the islets with an insulin-staining area similar to control autopsy pancreas (see Fig E4 in this article’s Online Repository at www.jacionline.org). Even in the 19-day-old infant (patient 2)