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

Consistent with previous reports,[6] 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.[6-9] 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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The study was funded by the Sigrid Jusélius Foundation (O.M.), the Academy of Finland (O.M.), the Folkhälsan Research Foundation (O.M.), the Helsinki University Hospital Research Funds (O.M. and M.T.), the Swedish Childhood Cancer Foundation (O.M.), the Foundation for Pediatric Research (O.M. and M.T.), the Finnish Medical Foundation (S.K.), and the Doctoral School in Health Sciences at the University of Helsinki (S.K.). The research was supported in part by the Intramural Research program of the National Institutes of Health, National Institute of Allergy and Infectious Diseases.

Disclosure of potential conflict of interest: P. Klemetti has received a grant from the Foundation for Pediatric Research for this work. T. Martelius has received a grant from Sanguin; lecture fees from MSD and CSL Behring; and travel grants from Octapharma, CSL Behring, Sanguin, Gilead, and MSD. L. D. Notarangelo has received board membership from the *Journal of Clinical Immunology*, *Clinical Immunology*, and *Frontiers in Immunology*; is employed by the National Institutes of Health and received royalties from UpToDate. M. Seppänen has received financial support for travel from CSL Behring and Octapharma for this work. M. Taskinen has received a grant from Helsinki University Hospital Research fund for this work. O. Mäkitie's institution has received grants from the Sigrid Jusélius Foundation, the Academy of Finland, the Folkhälsan Research Foundation, Helsinki University Hospital Research Funds, the Swedish Childhood Cancer Foundation, and the Foundation for Pediatric Research for this work. The rest of the authors state that they have no relevant conflict of interest.

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Available online March 9, 2017.
http://dx.doi.org/10.1016/j.jaci.2017.02.016

Allergic rhinitis increases the risk of driving accidents

To the Editor:

Allergic rhinitis (AR) disturbs patients' quality of life with consequences on their occupational and daily activities; it also reduces quality of sleep and induces daytime drowsiness,[1] which can increase the risk of driving accidents. Connor et al[2] showed that when people complained of feeling very drowsy while driving, the risk of having a traffic accident compared with a nondrowsy person was multiplied by 8.2. Some authors have hypothesized that drowsiness due to poor sleep may be a more common cause of accidents than alcohol and reported that studies are urgently needed.[3] Therefore, we conducted the "EVEIL" national survey. The main aim was to assess the consequences of AR on daytime awareness and driving and to identify through cluster analysis methodology the existence of a patient group at increased risk of car accidents on the basis of the features of their AR.

We conducted a cross-sectional observational national survey in primary care allergy medicine and general practice on a randomized sample stratified geographically (quotas method).

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[4] and awareness at the wheel by the Karolinska Sleepiness Scale (KSS) score.[5] 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 aware") to 9 ("very sleepy, considerable effort needed to remain awake and stop going to sleep"). An ascending hierarchical cluster analysis (Ward method)[6] 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% of the patients. The allergens, which were found in 61.0% of these patients, were predominantly pollens (79.3%), moulds and dust mites (44.1%), and animals (14.5%).

The EPWORTH score was 7.6 ± 5.4 (out of 24). On the basis of this score, 30.3% of the patients had moderate (25.9%; 95% CI, 24.5-27.3) or severe (4.4%; 95% CI, 3.7-5.0) drowsiness. The KSS score was 3.9 ± 1.8, which showed that not only were 39.4% (95% CI, 37.8-40.9) of the patients at risk of reduced awareness when driving, 24.4% were also at high risk of having an accident: 18.8% had signs of sleepiness, 3.6% felt sleepy but remained awake without efforts, and 2.0% felt sleepy and needed to make efforts to remain awake.

In addition, 63.8% of the patients described on questioning that their AR had an effect on driving, some of which had been dangerous including not having the right reflex in some situations (18.9%), having made an unusual driving error (13.6%), or falling asleep for a fraction of a second (9.5%). Almost one-fifth of the patients (17.5%) also reported that they had needed to stop on the edge of the road or even that they did not feel capable of driving (16.4%) and 0.7% reported they had a car accident.

The cluster analysis of the whole population using Ward's ascending hierarchy method identified 2 almost equivalent sized patient groups: cluster 1 (n = 1739 [47.7%]) and cluster 2 (n = 1910 [52.3%]). This methodology overcomes one of the limitations of the study of not having a control group. The comparisons of their features show that cluster 1 contained patients experiencing drowsiness and lack of awareness when driving, which was far more severe than in cluster 2: EPWORTH score 12.2 ± 3.4 versus 3.2 ± 2.6 ($P < .0001$) and KSS score: 4.8 ± 1.6 versus 3.1 ± 1.5 ($P < .0001$). The effect of AR on driving statistically differs between clusters 1 and 2. In particular, 85.2% versus 45.3% of the patients described that their AR had an effect on driving, 26.2% versus 12.4% that they had not the right reflex in some situations, 18.6% versus 9.7% that they made an unusual driving error, 15.2% versus 4.3% that they fell asleep for a fraction of a second, 23.7% versus 11.9% that they had needed to stop on the edge of the road, 23.5% versus 9.9% that they did not feel capable of driving, and 0.9% versus 0.6% reported that they had a car accident.

Cluster 1 could also be distinguished on the ARIA classification by more persistent (60.9% vs 51.9%; $P < .0001$) and moderate to 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[7]: 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[8] 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[9] 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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Disclosure of potential conflict of interest: P. Demoly has received consultancy fees from ALK, Stallergènes Greer, Circassia, Chiesi, ThermoFisherScientific, and Menarini. P. Maigret and I. E. Billon are employed by Menarini France. F.-A. Allaert's institution

has received a grant from Menarini for this work. F.-A. Allaert has personally received board membership from Cenbiotech, consultancy fees from Cenbiotech, payments for lectures from Servier, payment for manuscript from Urgo, and travel expenses from Cenbiotech.

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Available online March 9, 2017.
http://dx.doi.org/10.1016/j.jaci.2017.01.037

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*,[1] 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,[2-4] 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 hyperechoic 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 $CD4^+FOXP3^{hi}$ $CD25^{hi}$ T cells. Histologic evaluation 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)