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AARON L., THERBY A., VIARD J.P., LAHOULOU R., DUPONT B.

Successful medical treatment of *Candida albicans* in mechanical prosthetic valve endocarditis.

Scand. J. Infect. Dis., 35 (5), 351-352, 2003

(Services cités : Infectiologie, Immunologie Clinique Adulte)

Fungal prosthetic valve endocarditis is particularly serious, and is usually a result of nosocomial candidaemia. This report describes a patient with *Candida albicans* prosthetic valve endocarditis in whom surgery was believed to be contraindicated. After 45 d of amphotericin B, treatment was continued with fluconazole daily with a follow-up of 16 months, with no recurrent or adverse effects.

CAILHOL J., VIARD J.P., DUPONT B., AARON L.

Cutaneous and extracutaneous pyoderma gangrenosum associated with sigmoid adenocarcinoma.

Gastroentérol. Clin. Biol., 27 (10), 955-957, 2003

(Services cités : Infectiologie, Immunologie Clinique Adulte)

CAILHOL J., CALATRONI M.I., ROUDIÈRE L., AARON L., VIARD J.P.

Increased Incidence of Lung Neoplasms Among HIV-Infected Men and the Need for Improved Prevention.

J. Acq. Immun. Defic. Synd., 34 (2), 247-249, 2003

(Services cités : Infectiologie, Immunologie Clinique Adulte)

FRIEDMAN S., VILA G., EVEN C., TIMSIT J., BOITARD C., DARDENNES R., GUELFY J.D., MOUREN-SIMEONI M.C.

Alexithymia in insulin-dependent diabetes mellitus is related to depression and not to somatic variables or compliance.

J. Psychosom. Res., 55 (3), 285-287, 2003

(Services cités : U580, Psychiatrie Adulte, Immunologie Clinique Adulte, Pédo-Psychiatrie)

OBJECTIVES: To assess the prevalence of alexithymia in insulin-dependent diabetic mellitus (IDDM) outpatients. To examine whether alexithymia is associated with diabetic somatic variables, depression, and compliance. **METHOD:** Our sample comprised 69 diabetic outpatients followed in a university hospital. We assessed the prevalence of alexithymia (26-item Toronto Alexithymia Scale, TAS-26) and the relationships among alexithymia, depression (13-item Beck Depression Inventory, BDI-13), somatic diabetic variables (glycosylated hemoglobin, number of mild or severe hypoglycemia, somatic complications), and compliance (observer-rater scale completed by diabetologist). **RESULTS:** The prevalence of alexithymia in IDDM patients was low (14.4%). Alexithymia and depression, as measured by TAS-26 and BDI-13 scores, respectively, correlated with each other. Alexithymia was not correlated with glycemic control, somatic complications, or compliance. **CONCLUSION:** In our sample, alexithymia was related to depression and not to somatic factors or compliance.

MARCELIN A.G., AARON L., MATEUS C., GYAN E., GORIN I., VIARD J.P., CALVEZ

V., DUPIN N.

Rituximab therapy for HIV-associated Castleman disease.

Blood, 102 (8), 2786-2788, 2003

(Services cités : Immunologie Clinique Adulte)

To assess the clinical benefit of rituximab for HIV-associated Castleman disease, 5 patients infected with HIV with histologic-proven Castleman disease were prospectively enrolled to receive 4 infusions of rituximab. Clinical and biologic parameters (C-reactive protein, CD19 cell count, Kaposi sarcoma-associated herpesvirus [KSHV] viral load in peripheral blood mononuclear cells) were assessed before and at different time points following rituximab infusions. Two patients died very quickly after the beginning of rituximab therapy with no effect on both KSHV viral load and CD19 cell count. Three of 5 patients were considered in complete remission with no more clinical symptoms related to Castleman disease with a follow-up of 4 to 14 months. In 2 cases, clinical remission correlated with a dramatic decrease of KSHV viral load and C-reactive protein levels and a transitory but sharp decrease of CD19 cell count. In 2 responders, we observed an aggravation of Kaposi sarcoma. Our preliminary results suggest that rituximab may be effective in controlling Castleman disease in a subset of patients, although it may exacerbate concomitant Kaposi sarcoma.

ROUSSEL R., REIS A.F., DUBOIS-LAFORGUE D., BELLANNE-CHANTELOT C., TIMSIT J., VELHO G.

The N363S polymorphism in the glucocorticoid receptor gene is associated with overweight in subjects with type 2 diabetes mellitus.

Clin. Endocrinol., 59 (2), 237-241, 2003

(Services cités : Immunologie Clinique Adulte)

OBJECTIVE: A single nucleotide polymorphism (A1220G; N363S) in exon 2 of the glucocorticoid receptor gene (NR3C1), associated with increased sensitivity to glucocorticoids, was shown to be associated with obesity in nondiabetic subjects. Here, we investigated the impact of this variant on traits related to obesity and hyperglycaemia in subjects with type 2 diabetes mellitus. PATIENTS AND MEASUREMENTS: The N363S variant was screened by restriction fragment length polymorphism technique following DNA amplification by polymerase chain reaction in 369 French Caucasians with type 2 diabetes mellitus. RESULTS: Twenty subjects were found to be heterozygous for the variant (AG genotype frequency 0.0542). The prevalence of overweight [body mass index (BMI) > 25 kg/m²] was higher in AG carriers than in AA carriers (100% vs. 73%, P = 0.003). Moreover, the mean body weight and the BMI were higher in AG as compared to AA carriers, although only the body weight was significantly different between groups. However, when only the men were considered, a significantly higher BMI was observed in AG as compared to AA carriers: 30.0 4.8 vs. 27.3 4.6 kg/m² (BMI Z-score 1.28 1.38 vs. 0.55 1.17; P = 0.035). No evidence was found for an association of the N363S variant with parameters related to the severity of hyperglycaemia. CONCLUSIONS: The 363S allele of the N363S variant of NR3C1 is associated with the susceptibility to overweight in subjects with type 2 diabetes mellitus.

THERBY A., DUPONT B., TIMSIT J., MARTINOVIC J., CHALLIER S., AARON L., MAMZER-BRUNEEL M.F.

Disseminated candidiasis and pregnancy: case report in a diabetic woman and review of the literature.

J. Mycol. Med., 13 (1), 40-47, 2003

(Services cités : Transplantation & Réanimation Adulte, Laboratoire de Microbiologie, Infectiologie, Immunologie Clinique Adulte, Histo-Embryologie & Cytogénétique)

While nearly 25% of pregnant women develop candidal vaginitis, intra amniotic infections and especially systemic infections due to *Candida* are rare. Before presenting a review of the literature, we describe the case of a 27-year-old diabetic patient whose pregnancy was complicated by *Candida albicans* chorioamnionitis and disseminated candidiasis (yeasts in urine, bilateral acute pyelonephritis and intravenous catheter infection). This sepsis led to miscarriage, at 19 weeks' gestation, of an infected fetus with candidal pneumonia. Despite treatment with fluconazole followed by caspofungine-5 flucytosine for a total of 4 months, improvement was slow with the persistent presence of yeasts in urine and a very highly positive serology. Forty-two days after the end of antimycotic treatments, an hematogenous chondrocostal abscess developed, which required surgery and a new course of fluconazole. After a one year and a half follow-up, no relapse of candidal infection has occurred.

VELHO G., BELLANNE-CHANTELOT C., TIMSIT J.

MODY, a model of genotype/phenotype interactions in type 2 diabetes.

M S-Méd. Sci., 19 (8-9), 854-859, 2003

(Services cités : Immunologie Clinique Adulte)

Maturity onset diabetes of the young (MODY) is a subtype of familial diabetes mellitus characterised by early onset, autosomal dominant inheritance and primary defects of insulin secretion. Mutations in six known genes (the enzyme glucokinase and five transcription factors expressed in pancreatic P-cells) cause most of the MODY cases. This genetic heterogeneity is associated with metabolic and clinical heterogeneity making MODY an interesting model of genotype/phenotype interaction in diabetes.

VIARD J.P.

Syndromes lipodystrophiques des patients infectés par le VIH recevant un traitement antirétroviral.

Journ. Annu. Diabétol. Hotel-Dieu, 111-123, 2003

(Services cités : Immunologie Clinique Adulte)

2002

AARON L., LIDOVE O., YOUSRY C., ROUDIERE L., DUPONT B., VIARD J.P.

Human herpesvirus 8-positive castleman disease in human immunodeficiency virus-infected patients: the impact of highly active antiretroviral therapy.

Clin. Infect. Dis., 35 (7), 880-882, 2002

(Services cités : Immunologie Clinique Adulte, Infectiologie)

We report the case histories of 7 human immunodeficiency virus (HIV)-infected patients receiving highly active antiretroviral therapy (HAART) who had a diagnosis of Castleman disease. All 6 patients who were treated responded to chemotherapy; immune reconstitution was observed in 5 patients, but it did not prevent relapse of Castleman disease. However, the mean duration of survival observed in this series (48 months) was most probably due to immune reconstitution resulting from receipt of HAART, which reduced the mortality associated with HIV disease.

ASSAN R., BLANCHET F., FEUTREN G., TIMSIT J., LARGER E., BOITARD C., AMIEL C., BACH J.F.

Normal renal function 8 to 13 years after Cyclosporin A therapy in 285 diabetic patients.

Diabetes Metab. Res. Rev., 18 (6), 464-472, 2002

(Services cités : Immunologie Clinique Adulte, Laboratoire d'Immunologie)

BACKGROUND: Cyclosporin A (CyA) may induce acute nephrotoxicity. The question has been raised of the possible long-term unfavorable course of CyA-induced lesions. Advantage was taken of a large cohort of diabetic patients treated for several months using moderate CyA dosage to evaluate the long-term evolution of renal function in such patients. **METHODS:** Two hundred and eighty five recently diagnosed type 1 diabetic patients having received CyA for a mean of 19.9 months were monitored for 13 years, in parallel with 100 similar patients treated with insulin alone. **RESULTS:** In the CyA-treated group, a transient increase in creatinemia levels occurred during the first 18 months of treatment associated with a transient increase in renal vascular resistance. Both effects disappeared later on: creatinemia levels then remained normal. Inulin and p-aminohippurate (PAH) clearances remained normal throughout follow-up. Neither permanent renal failure nor progressive deterioration of renal function occurred in either group or in individual patients. A 10 to 12% increase in inulin and PAH clearance was elicited by IV amino acid infusion at 7 to 10 years, a finding consistent with a normal renal functional reserve. Patients with moderate kidney lesions on biopsy at 1 year had normal and stable clearance values at 7 to 13 years. The prevalence of arterial hypertension and retinopathy was lower in the CyA-treated group than in the control group, possibly because of the tighter metabolic control obtained in the CyA group. **CONCLUSION:** These results suggest that low-dose CyA treatment combined with thorough monitoring does not result in long-term renal dysfunction.

BOITARD C.

Insulin secretion in type 2 diabetes: clinical aspects.

Diabètes Métab., 28 (6), S33-S38, 2002

(Services cités : Immunologie Clinique Adulte)

Type 2 diabetes is a complex disease that involves insulin secretion abnormalities and defects in the action of insulin on its target tissues. Insulin resistance alone is not sufficient to lead to type 2 diabetes in the absence of a beta-cell defect. Patients with impaired glucose tolerance or in the early stages of type 2 diabetes always present with beta-cell secretion defects. In the early stages of type 2 diabetes, abnormalities in the physiological biphasic insulin secretion are already encountered, with very often a loss of the first phase insulin secretion. In this review, we discuss the methods to evaluate beta-cell function and their limitations, then their relationship with genetic knowledge. Currently, it is still impossible, in the absence of biological parameters characterizing the etiology of type 2 diabetes, to precisely correlate the insulin-secretion tests with the diagnosis of the disease. Autoimmune type 1 diabetes appears a useful model to study type 2 diabetes. The availability of individual genetic mapping will permit a reliable clinical evaluation and interpretation of tests of insulin secretion in the future.

BOITARD C.

The origin of type 1 diabetes: an autoimmune disease ?

Diabètes Métab., 28 (4 Pt 1), 263-265, 2002

(Services cités : Immunologie Clinique Adulte)

LEPERCQ J., HAUGUEL-de-MOUZON S., TIMSIT J., CATALANO P.M.

Fetal macrosomia and maternal weight gain during pregnancy.

Diabetes Metab., 28 (4 Part 1), 323-328, 2002

(Services cités : Immunologie Clinique Adulte)

Background: To calculate an adjusted maternal weight gain during pregnancy including infant and placental weights to the actual weight gain and secondarily examine its influence on the occurrence of fetal macrosomia.

WEISS L., BURGARD M., CAHEN Y.D., CHAIX M.L., LAUREILLARD D., GILQUIN J., PIKETTY C., VIARD J.P., KAZATCHKINE M.D., GIRARD P.M., ROUZIUX C.

Immunological and virological features of HIV-infected patients with increasing CD4 cell numbers despite virological failure during protease inhibitor-based therapy.

HIV Med., 3 (1), 12-20, 2002

(Services cités : Immunologie Clinique Adulte, Laboratoire de Microbiologie)

OBJECTIVES: To investigate the extent of functional T cell recovery and to characterize plasma virus and virus producing cells in patients with increasing CD4 cell counts despite virological failure during protease inhibitor (PI) based therapy. METHODS: The study group included 13 patients who were treated for at least 12 months with a PI based regimen and were selected on the basis of a sustained immunological response (increase of > 70 CD4 cells/ μ mgr;L) despite virological failure (< 1 log₁₀ copies/mL decrease in HIV-1 RNA plasma levels). RESULTS: Compared to a historical series of 11 complete responders with less advanced disease, the proportion of memory CD4 T cells was significantly higher (67.8 ± 17.8 vs. 52.8 ± 11.0 ; $P=0.045$) and the proportion of naive CD4 T cells significantly lower (30.5 ± 14.8 vs. 45.0 ± 10.4 , $P=0.021$) in patients who were immunological responders/virological nonresponders. In those patients, ongoing viral replication was associated with a strong activation of circulating CD8 T lymphocytes; interleukin-2 production remained decreased. CD4 T cell reactivity to cytomegalovirus proteins was observed in nine of 11 patients tested. In the study group, the proportion of infectious virus present in plasma as well as the levels of intracellular viral replication were similar to those measured in untreated patients. Virological failure in this group of patients probably resulted from pre-existing mutations in the reverse transcriptase gene. CONCLUSIONS: This study of patients with increasing CD4 cell numbers despite virological failure shows the persistence of immune activation and partial immune restoration with no evidence of specific viral dynamics in vivo.

2001

DELRIEU O., DUBOIS-LAFORGUE D., TIMSIT J., TOURNIER-LASSERVE E., CAILLAT-ZUCMAN S.

A dinucleotide repeat polymorphism at the poly(adp-ribose) polymerase gene is not associated with predisposition to type 1 diabetes in french caucasians.

J. Autoimmun., 17 (2), 137-140, 2001

(Services cités : Laboratoire d'Immunologie, U025, Immunologie Clinique Adulte)

The poly (ADP-ribose) polymerase (PARP) is a nuclear enzyme that detects and binds DNA strand breaks. Excessive PARP activation leads to the death of mice islet beta -cells by depleting cellular energy reserves. On the other hand, PARP-mutant mice are resistant to streptozotocine-induced diabetes, and in the non-obese diabetic (NOD) mouse model, treatment with nicotinamide, a PARP inhibitor, protects islet cells against cytotoxic actions in vitro and results in a decreased incidence of type I diabetes. PARP gene in human is located within a recently identified type I diabetes-susceptibility region on chromosome 1q41-42, and contains a polymorphic CA dinucleotide repeat in the promoter region. To consider the putative involvement of PARP polymorphism in predisposition to type 1 diabetes, we performed

genotyping for the various alleles of the CA dinucleotide repeat in 158 unrelated French Caucasian patients with type I diabetes and 193 ethnically-matched healthy controls. We found no significant difference of PARP alleles. distribution between patients and controls, even after stratification of the patients according to HLA class II genotype or to age at disease onset. Our results suggest that this PARP polymorphism does not influence susceptibility to type I diabetes in French Caucasians. (C) 2001 Academic Press. [References: 15]

DUBOIS-LAFORGUE D., HENDEL H., CAILLAT-ZUCMAN S., ZAGURY J.F., WINKLER C., BOITARD C., TIMSIT J.

A common stromal cell-derived factor-1 chemokine gene variant is associated with the early onset of type 1 diabetes.

Diabetes, 50 (5), 1211-1213, 2001

(Services cités : Immunologie Clinique Adulte, Laboratoire d'Immunologie)

presence of the SDF1-3'A allele was associated with a 5-year reduction in the age at onset of diabetes (P = Type 1 diabetes results from the autoimmune destruction of pancreatic beta -cells. Although the disease shows a strong association with HLA class II alleles, other genes may influence the initiation or the rate of progression of the autoimmune process. The recruitment of mononuclear cells within the islets of Langerhans is a critical step in the pathogenesis of the disease. Because chemokines are cytokines that promote migration of mononuclear cells, we hypothesized that polymorphisms in chemokine receptor or chemokine genes, CCR5 and SDF1, may be involved in susceptibility to or clinical expression of type 1 diabetes. The frequencies of the CCR5-Delta 32 and SDF1-3'A (801G -->A in the 3' untranslated region) variants were similar in 208 unrelated Caucasian patients with type 1 diabetes and in 120 Caucasian control subjects. They were not modified after stratification for the predisposing HLA-DR3 and -DR4 haplotypes, However, the SDF1-3'A variant was strongly associated with early onset (<15 years) of the disease (odds ratio 2.6, P = 0.0019), On average, the presence of the SDF1-3'A allele was associated with a 0.0067), Our results suggest that stromal cell-derived factor-1 may be implicated in the aggressiveness of the autoimmune process leading to type 1 diabetes, These preliminary data require replication in other populations. [References: 20]

GOUGEON M.L., ROUZIOUX C., LIBERMAN I., BURGARD M., TAOUFIK Y., VIARD J.P., BOUCHENAF K., CAPITANT C., DELFRAISSY J.F., LEVY Y.

Immunological and virological effects of long term il-2 therapy in hiv-1-infected patients.

AIDS, 15 (13), 1729-1731, 2001

(Services cités : Immunologie Clinique Adulte, Laboratoire de Microbiologie)

We report the long-term outcome of 27 HIV-infected patients treated for over 3 years with IL-2 and binucleoside analogues. These patients experienced a sustained increase in CD4 cells and a decrease of proviral DNA with infrequent IL-2 cycles. In three cases, virus could not be isolated from activated peripheral cells. A high frequency of HIV-1-specific memory CD4 T cells was found in the patients studied. IL-2 maintains specific effector cells and reduces the pool of infected cells in patients, albeit treated only with binucleosides. [References: 5]

GRIMALDI A., SACHON C., TIMSIT J.

Insulin doses adaptation with insulin lys-pro in external pump.

Diabetes Metab., 27 (3), 386-387, 2001

(Services cités : Immunologie Clinique Adulte)

GUILLAUSSEAU P.J., MASSIN P., DUBOIS-LAFORGUE D., TIMSIT J., VIRALLY M., GIN H., BERTIN E., BLICKLE J.F., BOUHANICK B., CAHEN J., CAILLAT-ZUCMAN S., CHARPENTIER G., CHEDIN P., DERRIEN C., DUCLUZEAU P.H., GRIMALDI A., GUERCI B., KALOUSTIAN E., MURAT A., OLIVIER F., PAQUES M., PAQUIS-FLUCKLINGER V., POROKHOV B., SAMUEL-LAJEUNESSE J., VIALETES B.

Maternally inherited diabetes and deafness: a multicenter study.

Ann. Intern. Med., 134 (9), 721-728, 2001

(Services cités : Immunologie Clinique Adulte, Laboratoire d'Immunologie)

Background: Maternally inherited diabetes and deafness (MIDD), which is seen in 0.5% to 2.8% of patients with type 2 diabetes mellitus, is related to a point mutation at position 3243 of mitochondrial (mt) DNA. Its clinical description is incomplete. Objective: To study the clinical presentation and complications of diabetes in patients with MIDD and to identify clinical characteristics that may help select diabetic patients for mtDNA mutation screening. Design: Multicenter prospective descriptive study. Setting: 16 French departments of internal medicine, diabetes and metabolic diseases, or both. Patients: 54 patients with type 2 diabetes mellitus and the mtDNA 3243 mutation. Measurements: Characteristics of diabetes, metabolic control (glycosylated hemoglobin level), complications of diabetes, and Involvement of other organs. Results: On average, patients with MIDD were young at diabetes onset and presented with a normal or low body mass index. None were obese. Seventy-three percent of probands had a maternal family history of diabetes. Diabetes was non-insulin-dependent at onset in 87% of patients; however, 46% of patients had noninsulin-dependent disease at onset but progressed to insulin therapy after a mean duration of approximately 10 years. Neurosensory hearing loss was present in almost all patients. Eighty-six percent of patients who received an ophthalmologic examination had macular pattern dystrophy (a specific retinal lesion), Forty-three percent of patients had myopathy, 15% had cardiomyopathy, and 18% (9 of 51) had neuropsychiatric symptoms. Although the prevalence of diabetic retinopathy was 8% among patients who received an ophthalmologic examination, lower than expected after a mean 12-year duration of diabetes, prevalence of kidney disease was 28%. This suggests that a specific renal involvement was the result of mitochondrial disease. Conclusions: Maternally inherited diabetes and deafness has a specific clinical profile that may help identify diabetic patients for mtDNA testing. [References: 46]

KIRK O., MOCROFT A., PRADIER C., BRUUN J.N., HEMMER R., CLOTET B., MILLER V., VIARD J.P., PHILLIPS A.N., LUNDGREN J.D.

Clinical outcome among hiv-infected patients starting saquinavir hard gel compared to ritonavir or indinavir.

AIDS, 15 (8), 999-1008, 2001

(Services cités : Immunologie Clinique Adulte)

Objective: To compare the clinical response among patients who initiate protease inhibitor therapies with different virological potency. Design: We analysed patients who started indinavir, ritonavir or saquinavir hard gel capsule (hgc) as part of at least triple therapy during prospective follow-up within the EuroSIDA study. Methods: Changes in plasma viral load (pVL) and CD4 cell count from baseline were compared between treatment groups. Time to new AIDS-defining events and death were compared in Kaplan-Meier models, and Cox models were established to further assess differences in clinical progression (new AIDS/death). Adjustment was made for differences in baseline parameters, in particular pVL, CD4 cell count, and region of Europe. Results: A total of 2708 patients (median follow-up: 30 months) were included, of which 556

started ritonavir (21%), 1342 indinavir (50%), and 810 saquinavir hgc (30%). The three groups were fairly evenly balanced at baseline regarding CD4 count, previous diagnosis of AIDS and pVL. After 12 months, the median changes in CD4 cell count were 90, 96 and 74 x 10(6) cells/l, respectively; P < 0.001, the proportions of patients with pVL < 500 copies/ml were 47, 54 and 41%; P < 0.001, and the proportions with clinical progression were 11.9, 9.2 and 11.9%, respectively; P = 0.20 (log-rank test). In multivariate models the relative risk of clinical progression for indinavir compared with saquinavir hgc was: 0.77 (0.60-0.99); P = 0.043, and for ritonavir 0.83 (0.62-1.11); P = 0.20. Conclusions: Saquinavir hgc was associated with an inferior long-term clinical response relative to indinavir, which was consistent with the observed differences in virological and immunological responses. (C) 2001 Lippincott Williams & Wilkins. [References: 32]

LEPERCQ J., TAUPIN P., DUBOIS-LAFORGUE D., DURANTEAU L., LAHLOU N., BOITARD C., LANDAIS P., HAUGUEL-de-MOUZON S., TIMSIT J.

Heterogeneity of fetal growth in type 1 diabetic pregnancy.

Diabetes Metab., 27 (3), 339-344, 2001

(Services cités : Biostatistique, Immunologie Clinique Adulte)

Objective: To investigate the frequency of macrosomia in an homogeneous cohort of type 1 diabetic mothers and to analyze the influence of maternal factors and glycemic control on the incidence of fetal macrosomia. Material and methods: Fifty-five consecutive type 1 diabetic first pregnancies were prospectively studied. Macrosomia was defined by a ponderal index above the 90(th) percentile. Venous cord blood levels of insulin, C peptide and leptin were measured at delivery. The influence of HbA1c levels and other maternal variables on the occurrence of macrosomia and on the ponderal index was assessed using a stepwise regression logistic model. Results: The mean (+/- SD) birth weight was 3482 (+/- 497) g at 37.4 +/- 1.0 weeks gestation. Macrosomia occurred in 29 cases (53.7%). Feta I insulin, C peptide and leptin levels were significantly higher in macrosomic than in non macrosomic infants. Maternal age, duration of diabetes, pregravid body mass index, parity, weight gain during pregnancy, presence of a microangiopathy, nephropathy, smoking habits, gestational hypertension or preeclampsia, and HbA1c levels throughout pregnancy did not differed between mothers of macrosomic and non macrosomic infants. In the stepwise analysis none of these covariates was explanatory of the ponderal index. Conclusions: The frequency of macrosomia remains very high in infants of type 1 diabetic mothers despite a reasonable degree of glycemic control. The variability of the fetal growth response to mild hyperglycemia prompts for the identification of other factors involved in the modulation of fetal growth. [References: 29]

RAKOTOAMBININA B., MEDIONI J., RABIAN C., JUBAULT V., JAIS J.P., VIARD J.P.

Lipodystrophic syndromes and hyperlipidemia in a cohort of hiv-1-infected patients receiving triple combination antiretroviral therapy with a protease inhibitor.

J. Acq. Immun. Defic. Synd., 27 (5), 443-449, 2001

(Services cités : Biostatistique, Immunologie Clinique Adulte)

Objectives: To assess the frequency and features of lipodystrophic syndromes in HIV-1-infected patients receiving highly active antiretroviral therapy (HAART) with a protease inhibitor (PI), and examine whether clinical and biologic abnormalities are always associated in these conditions. Methods: Retrospective-prospective single-center observational study of 175 patients. Comparisons for continuous variables by t-test and paired t-test, and Kaplan-Meier analysis of

time to onset of lipodystrophy were performed. Results: In all, 51 patients (29%) had morphologic changes, after a mean HAART duration of 20.0 +/- 6.1 months, and were categorized into pure lipoatrophy (n = 16), mixed syndrome (truncal fat accumulation and face or limb lipoatrophy) (n = 30) or pure truncal fat accumulation (n = 5). Because of the small number, the latter group was not analyzed statistically. No differences were found among patients with lipoatrophy, mixed syndrome, or no lipodystrophy, in terms of gender, CD4 count, and HIV RNA plasma load at time of HAART initiation, nor in response to treatment. Patients with a mixed syndrome were older. Patients with lipoatrophy had longer duration of HIV disease, pre-HAART exposure to nucleoside analog therapy, and HAART. Baseline and pre-HAART fasting triglyceride levels were higher in patients who developed lipoatrophy, whereas weight and fasting cholesterol were higher in patients who developed a mixed syndrome. After 12 and 24 months on HAART, triglycerides and cholesterol rose significantly in all patients, independently of lipodystrophy, whereas these parameters were not increased during nucleoside analog therapy. Conclusions: Nucleoside analog exposure appears as a risk factor for lipoatrophy. Age and nutritional status (reflected by baseline weight, triglycerides and cholesterol) may influence the evolution to lipoatrophy or a mixed syndrome. Hyperlipidemia is observed in the absence of lipodystrophy and depends on PI exposure. [References: 32]

TIMSIT J., VELHO G.

Un diabète de type MODY.

Journ. Annu. Diabétol. Hôtel-Dieu, 151-158, 2001

(Services cités : Immunologie Clinique Adulte)

VIARD J.P., MOCROFT A., CHIESI A., KIRK O., ROGE B., PANOS G., VETTER N., BRUUN J.N., JOHNSON M., LUNDGREN J.D.

Influence of age on cd4 cell recovery in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy: evidence from the eurosida study.

J. Infect. Dis., 183 (8), 1290-1294, 2001

(Services cités : Immunologie Clinique Adulte)

Influence of age on the CD4 cell response to highly active antiretroviral therapy (HAART) was examined in 1956 patients (median age, 37.2 years) in the EuroSIDA study. Median initial CD4 cell count was 192 X 10(6) cells/L, follow-up was 31 months, and time to maximum CD4 cell response was 20 months. Age groups were not different for baseline CD4 cell count, baseline human immunodeficiency virus RNA load, or treatment history. CD4 cell increase, stratified by age quartiles, differed during months 3-36 of HAART (P =.023). Maximum CD4 cell increase from start of HAART differed by age group (P =.0003), as did maximum CD4 cell count (P < 10(-4)). Multivariate analysis confirmed the inverse relationship between age and maximum CD4 cell response (P =.023). Time to a CD4 increase of >200 X 10(6) cells/L was shorter for patients in the younger age groups (P =.0026), as confirmed by multivariate analysis (P < 10(-4)).

Younger age may favor CD4 cell restoration because of preserved thymic function. [References: 16]

YE W.Z., REIS A.F., DUBOIS-LAFORGUE D., BELLANNE-CHANTELOT C., TIMSIT J., VELHO G.

Vitamin d receptor gene polymorphisms are associated with obesity in type 2 diabetic subjects with early age of onset.

Eur. J. Endocrinol., 145 (2), 181-186, 2001

(Services cités : Immunologie Clinique Adulte)

Objective: Allelic variations in the vitamin D receptor (VDR) gene were reported to modulate insulin secretion in response to glucose. VDR was investigated as a candidate gene for type 2 diabetes mellitus (T2DM). Method: Four single nucleotide polymorphisms (SNPs) in intron 8 (BsmI, Tru9I, ApaI) and exon 9 (TaqI) of the VDR gene were examined in 309 unrelated French subjects with T2DM and 143 controls. Results: The distribution of alleles and genotypes of the four SNPs was similar in patients and controls. However, in patients whose age at diagnosis of diabetes was less than or equal to 45 years, homozygous subjects for the T-allele of the TaqI SNP had a higher body mass index (BMI) (31.7 ± 6.7 kg/m²), $P = 0.0058$) and an increased prevalence of obesity (81%, $P = 0.005$) with respect to heterozygous subjects (27.9 ± 5.0 kg/m²; 46%) or homozygous subjects for the t-allele (27.7 ± 5.0 kg/m²; 52%). Similar results were observed for homozygous subjects for the b-allele of the BsmI SNP Logistic regression analysis demonstrated that TT homozygosity was independently associated with obesity in these subjects (odds ratio, 4.64; 95% confidence interval (CI), 1.64-14.76: $P = 0.0056$). Conclusion: VDR is not a major gene for T2DM in French Caucasians. However, polymorphisms in the VDR gene are associated with the susceptibility to obesity in subjects with early-onset T2DM. The pathophysiological mechanisms of these associations remain unexplained, but they could be related to a direct effect of vitamin D in adipocyte differentiation and metabolism, or to an indirect effect by modulation of insulin secretion. [References: 34]

YE W.Z., DUBOIS-LAFORGUE D., BELLANNE-CHANTELOT C., TIMSIT J., VELHO G.

Variations in the vitamin d-binding protein (gc locus) and risk of type 2 diabetes mellitus in french caucasians.

Metabolism, 50 (3), 366-369, 2001

(Services cités : Immunologie Clinique Adulte)

Electrophoretic variants of the vitamin D-binding protein (DBP) have been reported to be associated with type 2 diabetes mellitus (DM) or with prediabetic phenotypes in several non-Caucasian populations. Two frequent missense polymorphisms at codons 416 (Asp --> Glu) and 420 (Thr --> Lys) are the genetic basis for the 3 common electrophoretic variants of DBP (Gc1F, Gc1S, and Gc2) and the resulting circulating phenotypes (Gc1F/Gc1F, Gc1F/Gc1S, Gc1S/Gc1S, Gc1F/Gc2, Gc1S/Gc2, and Gc2/Gc2). In this study, we investigated the association of these polymorphisms with type 2 DM in French Caucasian subjects. Variations at codons 416 and 420 were examined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Allele frequencies at both codons did not differ in type 2 DM patients and in control subjects (Asp416: 42.4% v 46.2%, respectively, $P = .33$; Lys420: 25.5% v 29.0%, respectively, $P = .31$). Distribution of genotypes at both codons, of the haplotypes defined by the 2 codons, and of the DBP phenotypes defined by the haplotypes were also similar in diabetic and control subjects. In conclusion, our study suggests that genetic variants of the DBP gene are not associated with the susceptibility to type 2 DM in French Caucasians. Copyright 2001 by W.B. Saunders Company

2000

BOITARD C.

Immunomodulation.

M S-Méd. Sci., 16 (12), 1340-1345, 2000

(Services cités : Immunologie Clinique Adulte)

The study of activation and amplification mechanisms that characterize immune responses is a key contribution to immunomodulation. Many immunosuppressive drugs which target calcineurin inhibit lymphocyte proliferation. This precludes inducing Immune tolerance which, however, is an unquestioned goal of clinical immunology. New strategies focus on inducing immune tolerance by interfering with structures involved in antigen recognition either on antigen presenting cells or on lymphocytes. Targeting the T cell receptor and associated structures (CD3, CD4, CD8) or antigen presenting structures (major histocompatibility complex class II molecules) has proved efficient in inducing tolerance. Altered peptides ligands has seemingly been developed in order to interfere with T cell activation through the T cell receptor. Other approaches include targeting costimulatory structures (CD28/B7, CD40/CD40 ligand) or regulatory circuits involving cytokines, chemokines and their receptors. The molecular characterization of activated and tolerant lymphocytes is an achievable goal that will help defining new targets of immunomodulation in the coming years. [References: 20]

CHAILLOUS L., LEFEVRE H., THIVOLET C., BOITARD C., LAHLOU N., ATLAN GEPNER C., BOUHANICK B., MOGENET A., NICOLINO M., CAREL J.C., LECOMTE P., MARECHAUD R., BOUGNERES P., CHARBONNEL B., SAI P.

Oral insulin administration and residual beta-cell function in recent-onset type 1 diabetes: a multicentre randomised controlled trial.

Lancet, 356 (9229), 545-549, 2000

(Services cités : Immunologie Clinique Adulte)

Background Oral administration of autoantigens can slow the progression of beta-cell destruction in non-obese diabetic mice. We investigated whether oral administration of recombinant human insulin could protect residual beta-cell function in recent-onset type 1 diabetes. Methods We enrolled 131 autoantibody-positive diabetic patients aged 7-40 years within 2 weeks of diagnosis (no ketoacidosis at diagnosis, weight loss <10%, polyuria for <6 weeks). They were randomly assigned 2.5 mg or 7.5 mg oral insulin daily or placebo for 1 year, in addition to subcutaneous insulin therapy. Serum C-peptide concentrations were measured in the fasting state and after stimulation, to assess beta-cell function. Autoantibodies to beta-cell antigens were assayed. Analyses were by intention to treat. Findings Baseline C-peptide and haemoglobin A(1c) concentrations were similar in the three groups. During follow up, there were no differences between the groups assigned 2.5 mg or 7.5 mg oral insulin or placebo in subcutaneous insulin requirements, haemoglobin A(1c) concentrations, or measurements of fasting (mean at 12 months 0.18 [SD 0.17], 0.17 [0.17], and 0.17 [0.12] nmol/L) or stimulated C-peptide concentrations (glucagon-stimulated 0.39 [0.38], 0.37 [0.39], and 0.33 [0.24] nmol/L; meal-stimulated 0.72 [0.60], 0.49 [0.49], and 0.57 [0.51] nmol/L). Neither age nor C-peptide concentration at entry influenced treatment effects. No differences were seen in the time-course or titres of antibodies to insulin, glutamic acid decarboxylase, or islet antigen 2. Interpretation At the doses used in this trial, oral administration of insulin initiated at clinical onset of type 1 diabetes did not prevent the deterioration of beta-cell function. [References: 30]

DUBOIS-LAFORGUE D., CAILLAT-ZUCMAN S., BOITARD C., TIMSIT J.

Clinical characteristics of type 2 diabetes in patients with mutations of HFE.

Diabetes Metab., 26 (1), 65-68, 2000

(Services cités : Immunologie Clinique Adulte, Laboratoire d'Immunologie)

Genetic hemochromatosis (GH) is associated with two mutations of the HFE gene (Cys282Tyr and His63Asp). Heterozygosity for GH is associated with a mild increase in iron metabolism

parameters, and increased iron stores are associated with abnormal glucose tolerance and decreased insulin sensitivity in the general population. We have previously shown that the frequency of the two HFE mutations is not increased in patients with type 2 diabetes. However, to assess whether the presence of HFE mutations modulates the clinical presentation of type 2 diabetes, we studied the clinical characteristics and iron metabolism indexes according to the presence of the two mutations in 266 patients with type 2 diabetes. The Cys282Tyr mutation and the His63Asp mutation were present in 9.8% and 26% of the patients, respectively. Serum iron, transferrin saturation and ferritin concentrations were significantly increased in patients expressing either HFE mutations, compared to those without any mutation. There was no difference in the clinical characteristics in the two groups except that obesity was significantly less frequent in the patients with at least one mutation than in those without any mutation (27.6% vs 42.8%, $p = 0.02$). This finding suggests that, in the absence of obesity, HFE mutations, through the insulin resistance associated with the increase in iron stores, may contribute to the onset of type 2 diabetes. [References: 24]

DUBOIS-LAFORGUE D., LARGER E., TIMSIT J.

Is diabetes mellitus a sufficient condition to suspect hemochromatosis?

Diabetes Metab., 26 (4), 318-321, 2000

(Services cités : Immunologie Clinique Adulte)

Genetic Hemochromatosis (GH) is a highly prevalent autosomal recessive disorder, which outcome has been dramatically improved by early phlebotomy. Attempts to screen for the disease, using biological and genetic approaches, are currently under evaluation. Diabetes mellitus often complicates GH. However, as it occurs late in the course of the disease, in most cases when cirrhosis is already present, its usefulness for the screening of GH seems reduced. Diabetes mellitus, when isolated, appears also as a poor predictor of hemochromatosis. Indeed, the risk of being carrier of the disease is not increased in diabetic patients compared with non diabetic subjects. This risk is however highly enhanced by the co-existence of cirrhosis. Thus, in the face of a newly diagnosed diabetes mellitus, the search for hemochromatosis must be performed only when it associates with cirrhosis or with other evocative clinical conditions.

[References: 22]

DUBOIS-LAFORGUE D., TIMSIT J.

Type 1 diabetes and environment.

M S-Méd. Sci., 16 (10), 1045-1050, 2000

(Services cités : Immunologie Clinique Adulte)

Type 1 diabetes is a chronic autoimmune disease directed towards the pancreatic beta-cells and resulting in absolute insulin deficiency. Its long preclinical specific stage markers of ongoing autoimmune disease. Type 1 diabetes occurs in genetically predisposed individuals. However, in monozygotic twins, the concordance rate for the disease is only partial. This, and the rapid increase in the incidence of type 1 diabetes over the recent years suggest that environmental factors modulate the onset or the progression of the autoimmune process. Many putative agents, particularly viruses and diet factors, have been suspected, mainly on the basis of epidemiological studies. Among viruses, enteroviruses, particularly coxsackie, may either initiate the disease by materno-foetal infection or enhance autoimmune disease through bystander activation. A short duration of breast-feeding and the early introduction of cow's milk have been also epidemiologically involved in the onset of type 1 diabetes, but the mechanisms of this association remain elusive, The identification of environmental promoters of type 1 diabetes is a difficult task

because various agents may be implicated, and some may be also protective as shown in experimental models. Prospective studies in at-risk individuals are needed to identify common environmental triggers of type 1 diabetes before primary prevention may be envisaged.

[References: 30]

HENNEQUIN C., KAUFFMANN LACROIX C., JOBERT A., VIARD J.P., RICOUR C., JACQUEMIN J.L., BERCHE P.

Possible role of catheters in *Saccharomyces boulardii* fungemia.

Eur. J. Clin. Microbiol. Infect. Dis., 19 (1), 16-20, 2000

(Services cités : Immunologie Clinique Adulte, Laboratoire de Microbiologie, Gastroentérologie Pédiatrique)

Four cases of *Saccharomyces boulardii* fungemia, a very rare side effect of *Saccharomyces boulardii* therapy, are reported. The clinical impact of *Saccharomyces boulardii* infection appeared to be moderate. However, even though organ involvement was never demonstrated, septic shock with no other etiology was observed in one of our patients. All patients had an indwelling vascular catheter. Contamination of the air, environmental surfaces, and hands following the opening of a packet suggests that catheter contamination may have been a source of infection. To prevent catheter contamination it is recommended that packets or capsules of *Saccharomyces boulardii* be opened with gloves, outside the patient's room. [References: 20]

JUBAULT V., PACANOWSKI J., RABIAN C., VIARD J.P.

Interruption of prophylaxis for major opportunistic infections in HIV-infected patients receiving triple combination antiretroviral therapy.

Ann. Méd. Intern., 151 (3), 163-168, 2000

(Services cités : Immunologie Clinique Adulte)

Objective: To determine whether HIV-infected patients receiving highly active antiretroviral therapy (HAART) and recovering a CD4 cell number above $200 \times 10^6/l$ may safely discontinue primary and secondary prophylaxes for major opportunistic infections. Design: Retrospective study of a single-center, prospectively constituted cohort of 223 patients receiving HAART with a protease inhibitor, of whom 137 received at least one prophylaxis. Methods: Exhaustive informations on prophylaxis use, clinical and laboratory data were used to produce descriptive statistics on infectious events, duration of HIV infection, time on HAART, time to prophylaxis interruption, length of follow-up and biological values at relevant time points. Results: Fifty-one patients with a history of severe immunodepression (median CD4 nadir: $62 \times 10^6/l$), including 16 patients with CDC stage C infection, discontinued at least one prophylaxis. Primary or secondary *P. carinii* pneumonia prophylaxis was discontinued in 43 patients: 1 first episode of PCP occurred after 2 months but no other episode was recorded after a median follow-up of 16 months.

Toxoplasmosis primary or secondary prophylaxis, secondary cytomegalovirus prophylaxis and primary or secondary *M. avium* complex prophylaxes were discontinued in respectively 37, 5 and 5 patients, and no event was recorded after respective follow-ups of 16, 7 and 15 months. Nine secondary and 2 primary acyclovir prophylaxes were discontinued, and two events were observed after 1 and 19 months; no other event was noted after a follow-up of 22 months. Conclusion: Prophylaxis for opportunistic infections could be safely interrupted in most of these severely immunodeficient patients recovering a CD4 cell count above $200 \times 10^6/l$ on HAART. This confirms the efficiency of immune restoration and is beneficial to patients but, since 3 infectious events were recorded, caution should be taken before making a decision based on immunological and virological considerations. [References: 19]

JUBAULT V., PENFORNIS A., SCHILLO F., HOEN B., IZEMBART M., TIMSIT J., KAZATCHKINE M.D., GILQUIN J., VIARD J.P.

Sequential occurrence of thyroid autoantibodies and graves' disease after immune restoration in severely immunocompromised human immunodeficiency virus-1-infected patients.

J. Clin. Endocrinol. Metabol., 85 (11), 4254-4257, 2000

(Services cités : Immunologie Clinique Adulte)

We analyzed the kinetics of CD4 cells, human immunodeficiency virus (HIV) viral load, and autoantibodies in acquired immune deficiency syndrome patients with Graves' disease (GD) after immune restoration on highly active antiretroviral therapy (HAART; retrospective study). Five patients (median age, 41 yr) were diagnosed with GD after 20 (range, 14-22) months on HAART on the basis of clinical and biological hyperthyroidism, diffuse hyperfixation of thyroid scan, and the presence of anti-TSH receptor (anti-TSHR) antibodies (Ab). GD was diagnosed several months after the plasma HIV ribonucleic acid load became undetectable, when the CD4(+) cell count had risen from 14 (range, 0-62) to 340 (range, 163-460) x 10(6) cells/L. Antithyroid peroxidase (anti-TPO) and anti-TSHRab appeared 14 (range, 9-18) and 14 (range, 11-20) months after starting HAART and 12 (range, 6-15) and 11 (range, 9-17) months after the increase in CD4(+) cells. In 3 patients, TPOAb preceded TSHRab by 3-10 months. No other autoantibodies were detected. Thyroid antibodies were absent in a group of 55 HIV-1-positive patients with comparable response to HAART and no symptoms of hyperthyroidism (cross-sectional study). Thyroid-specific autoimmunity can occur upon immune restoration with HAART. Our observations suggest a relationship between thymus-dependent immune reconstitution after immunosuppression and autoimmunity and may provide insight into the pathophysiology of GD. [References: 39]

REIS A.F., YE W.Z., DUBOIS-LAFORGUE D., BELLANNE-CHANTELOT C., TIMSIT J., VELHO G.

Mutations in the insulin promoter factor-1 gene in late-onset type 2 diabetes mellitus.

Eur. J. Endocrinol., 143 (4), 511-513, 2000

(Services cités : Immunologie Clinique Adulte)

Objective: Insulin promoter factor-1 (IPF-1) is a transcription factor expressed in pancreatic beta cells. Following the identification of missense variants in the coding regions of the IPF-1 gene, in subjects selected for a strong family history of type 2 diabetes, the aim of our study was to evaluate the prevalence of these variants in the common form of type 2 diabetes. Methods: Three variants (C18R, Q59L and D76N) were screened by PCR-RFLP in a group of 296 unrelated French late-onset type 2 diabetic subjects consecutively recruited in a diabetes department of a university hospital, regardless of family history of diabetes. Results: The C18R and Q59L variants were each found in 0.37% of the diabetic patients, and in none of 147 controls. We did not detect the D76N variant, which was the most frequent variant in subjects with a strong family history of diabetes, in patients or controls. Conclusions: We have observed a combined prevalence of missense variants in the coding region of the IPF-1 gene of around 1%, in unselected patients with the common form of late-onset type 2 diabetes. The prevalence of these variants in subjects with a strong family history of type 2 diabetes had been found to be as high as similar to 6%. These differences in prevalence might be related to differences in the clinical profile of patients, such as age of onset of diabetes and associated obesity, as well as a family history of diabetes. [References: 14]

REIS A.F., YE W.Z., DUBOIS LAFORGUE D., BELLANNE CHANTELOT C., TIMSIT J., VELHO J.T.G.

Association of a variant in exon 31 of the sulfonylurea receptor 1 (sur1) gene with type 2 diabetes mellitus in french caucasians.

Hum. Genet., 107 (2), 138-144, 2000

(Services cités : Immunologie Clinique Adulte)

The sulfonylurea receptor (SUR1) of the pancreatic beta-cell ATP-sensitive potassium channel plays a key role in glucose-induced insulin secretion. The A-allele of a single nucleotide polymorphism (SNP) in exon 31 of the SUR1 gene (AG (G) under bar-->AG (A) under bar; Arg1273Arg) has previously been shown to be associated with hyperinsulinemia in nondiabetic Mexican-American subjects. Here, we have investigated the association of this SNP with type 2 diabetes mellitus (T2DM) in French Caucasian subjects. We have observed an increased frequency of the A allele (37.1% vs 27.6%, P=0.0048; odds ratio 1.54), of the AA genotype (15.7% vs 9.8%; P=0.025), and of the combined AA/AG genotypes (58.5% vs 45.5%, P=0.0098; odds ratio 1.69) in patients compared with controls. This association is stronger in the subgroup of patients with age of diagnosis of diabetes equal to or less than 45 years: A allele 43.2% (P=0.0003 compared with controls; odds ratio 1.99), AA genotype 21.4% (P=0.0032), and combined AA/AG genotypes 65.1% (P=0.0022; odds ratio 2.23). Unexpectedly, the G allele is strongly associated with arterial hypertension in obese diabetic subjects (GC vs AA odds ratio 19.97). In conclusion, we have observed an association of an SNP in exon 31 of the SUR1 gene with T2DM. These data reinforce the hypothesis that insulin secretion defects in T2DM might be at least partially related to allelic variations in the SUR1 gene. [References: 30]

ROUDIÈRE L., VIARD J.P.

Osteonecrosis of the hip, lipodystrophy and antiretroviral treatment.

AIDS, 14 (13), 2056, 2000

(Services cités : Immunologie Clinique Adulte)

TIMSIT J., DUBOIS-LAFORGUE D.

Should the occurrence of a first coronary event change the management of diabetes ?

Arch. Mal. Coeur Vaisseaux, 93 (Special Issue 4), 39-44, 2000

(Services cités : Immunologie Clinique Adulte)

The coronary morbi-mortality is particularly high in type 2 diabetes, which represents the vast majority of all diabetes. Hyperglycemia is an independent vascular risk factor in the short and long-term. The relationship between the degree of hyperglycemia and vascular risk is linear with no threshold effect. The occurrence of a first coronary event is an occasion, though late, to review the management of all risk factors in diabetic patients. In these patients, intensive insulin therapy administered in the acute phase of infarction reduces cardiovascular mortality by 30% at 1 and 3 years. There are no specific studies of secondary prevention by optimal therapy of diabetes, but, in the UKPDS, the treatment of hyperglycemia with sulfonylurea or insulin only marginally reduced the number of cardiovascular events. On the other hand, treatment of obese patients with metformin significantly reduced the incidence of myocardial infarction and of mortality diabetes related. These results, though observed with the same level of glycemic control as in the other treatment groups, suggest a cardio-protective effect of metformin itself. These beneficial effects should be weighed up against the potential risk of lactic acidosis which still limits the widespread use of metformin in with coronary heart disease patients. Follow-up studies show that diabetic with coronary heart disease patients do not receive all effective therapeutic inventions in

secondary prevention and that the treatment of hyperglycemia is often neglected. Close collaboration between cardiologists and diabetologists is necessary to improve the management of type 2 diabetes. [References: 33]

YAMAMOTO A.M., AMOURA Z., JOHANNET C., JERONIMO A.L.C., CAMPOS H., KOUTOUZOV S., PIETTE J.C., BACH J.F.

Quantitative radioligand assays using de novo-synthesized recombinant autoantigens in connective tissue diseases - new tools to approach the pathogenic significance of anti-rnp antibodies in rheumatic diseases.

Arthritis Rheum., 43 (3), 689-698, 2000

(Services cités : Immunologie Clinique Adulte)

Objective. To describe new assays for the detection and quantification of antibodies to RNPs in rheumatic diseases, using soluble nuclear antigens synthesized de novo in reticulocyte lysates, Methods. Sera from 381 patients with various rheumatic diseases, including 212 patients with systemic lupus erythematosus (SLE), were analyzed in order to evaluate the sensitivity and specificity of serum autoantibody reactivities to several recombinant soluble autoantigens: U1-A RNP, Sm-B, SSA/Ro 52 and SSA/Ro 60, SSB/La, and Ku, Radioligand assays (RLAs) were performed following the in vitro transcription and translation of each autoantigen from the corresponding complementary DNA, labeled with S-35-methionine. The radiolabeled protein was then bound by the specific serum autoantibody, forming immune complexes that were captured by protein A-Sepharose beads and quantified by counting the radioactivity. Results. Among the SLE patients, 44% were positive for anti-U1-A RNP activity, 34% for anti-Sm-B, 44% for anti-SSA (32% for Ro 52 and 46% for Ro 60), 32% for anti-SSB/La, and 11% for anti-Ku reactivities. SSA antibodies had a high frequency in patients with mixed connective tissue disease (MCTD) (80%); 65% these patient sera reacted, with Ro 52, 45% with Ro 60, and 45% with U1-A RNP, Twenty percent of the MCTD patients also exhibited antibodies to Sm-B and Ku, In patients with Sjogren's syndrome, anti-SSA was the main anti-RNP antibody (63%), together with SSB/La antibodies (44%), Among patients with inflammatory myopathy, only antibodies against Ro 52 (36%) and Ro 60 (36%) were present. These new RLA allowed observation of a strong correlation ($P < 0.0001$) between Sm-B antibody levels and the severity of SLE (as measured by the SLE Disease Activity Index), and establishment of a correlation between anti-U1-A RNP antibodies and the occurrence of SLE nephritis ($P < 0.02$), All RLAs were highly specific for the antigen tested and displayed, in the disease groups studied, a higher sensitivity than conventional immunodiffusion assays. Conclusion. These highly sensitive, specific, and quantitative RLAs represent new tools for the detection of autoantibodies to RNP antigens in rheumatic diseases, and may be useful for (differential) diagnosis in clinical practice. [References: 56]

ZYLBERBERG H., NALPAS B., POL S., BRECHOT C., VIARD J.P.

Is there a relationship between hepatitis c virus infection and antiretroviral-associated lipodystrophy ?

AIDS, 14 (13), 2055, 2000

(Services cités : Hépatologie Adulte, Immunologie Clinique Adulte)

1999

BIENVENU B., TIMSIT J.

Sauna-induced diabetic ketoacidosis.

Diabetes Care, 22 (9), 1584-1586, 1999

(Services cités : Immunologie Clinique Adulte)

CAREL J.C., BOUDALI S., BOUGNERES P., BOITARD C.

Immunologic approaches in the prevention and treatment of type 1 diabetes and endocrine autoimmune diseases.

Ann. Méd. Intern., 150 (4), 343-354, 1999

(Services cités : Immunologie Clinique Adulte)

CHATENOUD L.

Principles of action of biologic immunosuppressants.

Transplantation, 185-195, 1999

(Services cités : Immunologie Clinique Adulte)

DUBOIS-LAFORGUE D., CAREL J.C., BOURGNERES P.F., GUILLET J.G., BOITARD C.

T-Cell response to proinsulin and insulin in type 1 and pretype 1 diabetes.

J. Clin. Immunol., 19 (2), 127-134, 1999

(Services cités : Immunologie Clinique Adulte)

Insulin-dependent diabetes mellitus (IDDM) results from the selective destruction of pancreatic beta cells by a T cell-mediated autoimmune process. Insulin and proinsulin are the only known beta cell-specific autoantigens. Using short-term cultures of freshly isolated peripheral blood mononuclear cells, we evaluated T-cell responses to proinsulin and to insulin in IDDM patients and individuals at risk for IDDM. A proliferative T-cell response to proinsulin was observed in only of 16 recent-onset IDDM subjects and 2 of 12 long-standing IDDM subjects and was associated with a proliferative response to insulin. In contrast, 5 of 13 islet cell autoantibody-positive first-degree relatives of IDDM patients showed a proliferative response to proinsulin alone, 3 of 13 to insulin alone, and 1 of 13 to both insulin and proinsulin. Overall, 9 of 13 ICA-positive first-degree relatives responded to either proinsulin or insulin. We observed an inverse relationship between antiinsulin antibodies and T-cell responses to insulin in ICA-positive first-degree relatives but not in long-standing IDDM patients. Our data indicate that proinsulin is a major antigen in IDDM and, further, illustrate the difference between the autoimmune response to insulin and the immune response to exogenous insulin. [References: 52]

DUPIN N., de CERVENS V.R., GORIN I., CALVEZ V., PESSIS E., GRANDADAM M., RABIAN C., VIARD J.P., HURAUX J.M., ESCANDE J.P.

The influence of highly active antiretroviral therapy on AIDS-associated Kaposi's sarcoma.

Br. J. Dermatol., 140 (5), 875-881, 1999

(Services cités : Immunologie Clinique Adulte)

To assess the clinical and biological benefit of highly active antiretroviral therapy on AIDS-associated Kaposi's sarcoma (KS), 13 patients with AIDS-associated Kaposi's sarcoma (five pulmonary KS and eight cutaneous KS) were prospectively followed for a mean duration of 12 months. Six patients were treated with specific anti-KS chemotherapy before or simultaneously with the introduction of antiretroviral therapy. Clinical response was assessed according to the AIDS Clinical Trial Group (ACTG) criteria. CD4 cell counts, plasma HIV-1 RNA and human herpesvirus 8 (HHV-8) viraemia were measured at baseline and at different points. Among patients with pulmonary KS, we observed three complete responses (CR), one partial response (PR) and one progression. The median survival time after the diagnosis of pulmonary KS was 15

months with a median duration of the response after the discontinuation of specific chemotherapy for KS of 8 months, Among patients with cutaneous KS, we observed four CR, three PR and one stable response. A complete response was significantly associated with a reversal in HHV-8 viraemia (five of six vs. one of six; P = 0.02, Mann-Whitney test). [References: 14]

LARGER E., DUBOIS-LAFORGUE D., TIMSIT J.

Type 1 diabetes mellitus.

Presse Médicale, 28 (34), 1895-1903, 1999

(Services cités : Immunologie Clinique Adulte)

Positive diagnosis: Among the various diseases leading to chronic hyperglycemia, type 1 diabetes mellitus is distinctive by the presence of specific autoantibodies. The common form of type 1 diabetes mellitus is insulin-dependant diabetes, but type 1 diabetes may also present as non-insulin-dependent. In order to predict insulin-dependence and screen for associated autoimmune diseases, search for autoantibodies is required in all patients with diabetes, whatever the clinical presentation.

LEPERCQ J., LAHLOU N., TIMSIT J., GIRARD J., HAUGUEL-DE MOUZON S.

Macrosomia revisited: Ponderal index and leptin delineate subtypes of fetal overgrowth.

Amer. J. Obstet. Gynecol., 181 (3), 621-625, 1999

(Services cités : Immunologie Clinique Adulte)

OBJECTIVES: We sought to reanalyze the concept of fetal macrosomia with regard to the ponderal index and to investigate the role of insulin, insulinlike growth factor I, leptin, and maternal factors on birth size in a population of infants with nondiabetic mothers.

LEPERCQ J., TIMSIT J.

Diabetes and pregnancy.

Ann. Méd. Intern., 150 (5), 419-424, 1999

(Services cités : Immunologie Clinique Adulte)

The presence of insulin-dependent or non insulin-dependent diabetes mellitus in pregnant women has been associated with an adverse effect on the maternal and fetal outcomes of pregnancy. The incidence of obstetrical and diabetic complications is increased, and a continuum has been observed between maternal blood glucose levels and perinatal outcome. The incidence of congenital malformations, macrosomia and prematurity is increased in offspring of diabetic mothers. Programming and intensive collaborative follow-up improve the outcome of such pregnancies.

MOCROFT A., MADGE S., JOHNSON A.M., LAZZARIN A., CLUMECK N., GOEBEL F.D., VIARD J.P., GATELL J., BLAXHULT A., LUNDGREN J.D.

A comparison of exposure groups in the eurosida study: starting highly active antiretroviral therapy (haart), response to haart, and survival.

J. Acq. Immun. Defic. Synd., 22 (4), 369-378, 1999

(Services cités : Immunologie Clinique Adulte)

Background: Concerns have been raised that intravenous drug users may be less likely to start highly active antiretroviral therapy (HAART) and that adherence to therapy may be poor among this group of patients. Given the decreased mortality and incidence of AIDS-defining illnesses among patients-with HIV who start HAART, this may lead to a poorer prognosis among intravenous drug users. Purpose: To compare homosexual men, intravenous drug users, and

heterosexuals in EuroSIDA, a prospective European cohort of 7331 patients with HIV in terms of starting a HAART treatment regimen, immunologic and virologic response to therapy, and survival. Methods: 6645 patients were included in this analysis. Logistic regression and Cox proportional hazards models were used to investigate the factors associated with use of HAART regimens and survival following recruitment to the EuroSIDA study. Results: In a multivariate logistic regression model, intravenous drug users were significantly less likely to be receiving HAART at: recruitment to EuroSIDA (odds ratio [OR], 0.48; 95% confidence interval [CI], 0.37-0.62; $p < .0001$) when compared with homosexual men. Similarly, during follow-up, intravenous drug users were at a 27% reduced risk of starting HAART, after adjustment for other factors related to starting HAART (relative hazard [RH], 0.73; 95% CI, 0.64-0.82; $p < .0001$). There were no differences between heterosexual and homosexual patients, and similar results were found within regions of Europe (South, Central:and Northern). Among those patients who started HAART, there were no significant differences between exposure groups in CD4 lymphocyte count response to HAART or virologic response to HAART. After adjustment for factors related to survival, intravenous drug users were at a small, but nonsignificant increased risk of death compared with homosexuals (RH 1.16; 95% CI, 0.99-1.38; $p = .074$). Conclusions: Intravenous drug users were significantly less likely to start HAART, but among those who did, response to therapy was similar to that of other exposure groups. There were no differences in risk of death. If intravenous drug users continue to use HAART less commonly than other exposure groups, it may result in a poorer prognosis, a different spectrum of AIDS-defining illnesses, and differential long-term clinical needs. [References: 36]

VAXILLAIRE M., PUEYO M.E., CLEMENT K., FIET J., TIMSIT J., PHILIPPE J., ROBERT J.J., TAPPY L., FROGUEL P., VELHO G.

Insulin secretion and insulin sensitivity in diabetic and non-diabetic subjects with hepatic nuclear factor-1 alpha (maturity-onset diabetes of the young-3) mutations.

Eur. J. Endocrinol., 141 (6), 609-618, 1999

(Services cités : Immunologie Clinique Adulte)

Objective: To evaluate insulin secretion and sensitivity in affected (diabetes mellitus or impaired glucose tolerance; $n = 7$) and in unaffected (normal glucose tolerance: $n = 3$) carriers of hepatocyte nuclear factor-1 alpha (maturity-onset diabetes of the young-3 (MODY3)) gene mutations. Methods: Insulin secretion was assessed by an i.v. glucose tolerance test (IVGTT), hyperglycemic clamp and arginine test, and insulin sensitivity by an euglycemic hyperinsulinemic clamp. Results were compared with those of diabetic MODY3 (glucokinase-deficient) and control subjects. Results: The amount of insulin secreted during an IVGTT was decreased in affected MODY3 subjects (46 ± 24 (S.D.) pmol/kg body weight (BW)) as compared with values in MODY2 (120 ± 49 pmol/kg BW) and control (173 ± 37 pmol/kg BW; $P = 0.0004$) subjects. The amount of insulin secreted during a 10 mmol/l glucose clamp was decreased in affected MODY3 subjects (171 ± 78 pmol/kg BW) and MODY2 subjects (302 ± 104 pmol/kg BW) as compared with control subjects (770 ± 199 pmol/kg BW; $P = 0.0001$). Insulin secretion in response to arginine was decreased in affected MODY3 subjects. Milder and heterogeneous defects were observed in the unaffected MODY3 subjects: the amount of insulin secreted during the hyperglycemic clamp was 40-79% of that of controls, The response to arginine was abnormally delayed, Insulin sensitivity was decreased in diabetic but not in non-diabetic MODY3 subjects. Conclusions: Beta-cell dysfunction in response to glucose and arginine is observed in affected and unaffected MODY3 subjects. The MODY3 and MODY2 subtypes present different insulin secretion profiles. Secondary insulin resistance might

contribute to the chronic hyperglycemia of MODY3 patients and modulate their glucose tolerance. [References: 46]

VIRALLY M.L., TIMSIT J., CHANSON P., WARNET A., GUILLAUSSEAU P.J.

Insulin autoimmune syndrome: A rare cause of hypoglycaemia not to be overlooked.

Diabetes Metab., 25 (5), 429-431, 1999

(Services cités : Immunologie Clinique Adulte)

We report the case of a Caucasian patient with insulin autoimmune syndrome (IAS), defined as the association of hypoglycaemic attacks with insulin autoantibodies in individuals not previously treated with exogenous insulin. This rare syndrome (more than 200 published cases) has been reported mainly in Japan. Most affected patients present with other autoimmune disorders, most often Graves' disease. In most cases, insulin autoantibodies appear a few weeks after the beginning of treatment with a drug containing a sulphhydryl group. A significant increase in insulin and C-peptide plasma concentrations and the presence of other antiorgan antibodies are observed. The susceptibility haplotype is present in the Japanese population, which may account for the high frequency of IAS. Spontaneous remission is observed in 80% of cases, with cessation of hypoglycaemic attacks and disappearance of insulin autoantibodies some months after withdrawal of the drug. This rare cause of hypoglycaemia in Caucasian subjects should be considered in aetiologic investigation of spontaneous hypoglycaemia. [References: 10]