INTERSTITIAL LUNG DISEASES


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Interstitial lung diseases (ILDs) are inflammatory diseases characterized by slow and progressive destruction of alveolar-capillary functional units, often leading to respiratory failure and death. A first stage of alveolitis and a following stage of fibrosis provoke an anatomical distortion of the peripheral airways and the interstitium, and for their smoldering evolution and non-specificity of symptoms ILDs may remain undiagnosed and untreated for a long time. In this review we exploited the immunopathogenetic aspects and the therapeutical approaches to this frequently unrecognized and severe disease.

CHRONIC FATIGUE SYNDROME/MYALGIC ENCEPHALOMYELITIS: AN UPDATE

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Chronic Fatigue Syndrome (CFS), also referred to as Myalgic Encephalomyelitis (ME), is a disease of unknown origin. It is classified as Post Viral Fatigue Syndrome (PVFS) in the WHO International Classification of Diseases (ICD) and listed as sub-category at G93.3 under chapter G93, “other disorders of the brain”. ME/CFS is primarily an endemic disorder but occurs in both epidemic and sporadic forms. It affects all racial/ethnic groups and is seen in all socioeconomic strata. A diagnosis of CFS is a diagnosis of exclusion, meaning other medical conditions, including psychiatric disorders, must be first ruled out. CFS is diagnosed if there is no other explanation for the fatigue and if the other symptoms did not develop before the fatigue. The estimated worldwide prevalence of CFS is 0.4–1%. The disease predominantly affects young adults, with a peak age of onset of between 20 and 40 years, and women, with a female to male ratio of 6:1. Mean illness duration ranges from 3 to 9 years. The patho-physiological mechanism of CFS is unclear but the immunological pattern of CFS patients gleaned from various studies indicates that the immune system is chronically activated. Besides the role of environmental insults (xenobiots, infectious agents, stress) the genetic features of patients are studied to evaluate their role in triggering the pathology. At present there are no specific pharmacological therapies to treat the disease but a variety of therapeutic approaches have been described as benefiting patients. Treatment programs are directed at relief of symptoms, with the goal of the patient regaining some level of pre-existing function and well-being.
The immune system is a highly complex, intricately regulated group of cells whose integrated function is essential to health. The mast cell inflammatory response is characterized by an early phase with massive discharge of mediators stored in cytoplasmic secretory granules. Through multigranular/compound exocytosis and a late phase that involves generation of arachidonic acid metabolites and de novo synthesis of cytokines/chemokines and growth factors. Vitamins have been shown to have a protective effect on the body’s immune cells. Vitamin C and E are necessary in allergic disease treatment where mast cells are involved. In addition, ascorbic acid and pyridoxine are useful compounds for the treatment of inflammatory disorder of the respiratory airways. Here we revisited the inter-relationship between vitamins and mast cells.
Limited joint mobility is frequently observed in elderly people and in patients suffering from diabetes, who represent a growing segment of the population of western countries. Our review wishes to offer the “state of art” about this interesting topic, which may have important clinical implications, leading to impairment of both basic and instrumental activities of daily living. The main causes of a reduced range of motion are degenerative joint diseases and increased stiffness of collagen tissue. The main biochemical abnormality, common to aging and diabetes, is the non-enzymatic glycosilation of collagen, with advanced glycation end product (AGE) formation, which in turn leads to an increase of collagen cross-links. The most extensive accumulation of AGEs occurs in tissues that contain proteins with low turnover, such as the collagen in the extracellular matrix of articular capsule, ligaments and muscle-tendon units. The increase in collagen cross-linking alters the mechanical properties of these tissues with a decrease in elasticity and tensile strength, and an increase in mechanical stiffness. Besides this, AGEs react with specific cell surface receptors (RAGEs). The engagement of the ligand by RAGEs triggers cell-specific signalling, resulting in enhanced generation of reactive oxygen species and sustained up-regulation of pro-inflammatory mediators and adhesion molecules. An appropriate control of the glucose levels and a diet rich in antioxidant agents are recommended in patients with diabetes. Stretching and strengthening programmes are widely used, in order to prevent and to reduce joint stiffness, but the improvements with physiotherapy are little and short-lasting. Several drugs, which can interfere with AGE formation and removal, or with the cellular effects of AGEs, are under study (among them pyridoxamine, an active form of Vitamin B6, AGE-breaker compounds, glucosamine, rutin and derivatives, soluble RAGE isoforms, and statins). In experimental animal models, these drugs are effective in reducing diabetic complications due to AGE formation; however, further study is necessary before their extensive use in the clinical setting.
Bone resection is the choice treatment of malignant bone tumors. Tumor prosthesis is one of the most common solutions of reconstruction following resection of bone tumor located to the metaphysis of long bones. Periprosthetic infections are a frequent complication of limb-salvage surgery which is largely due to prolonged and repeated surgeries, as well as to the immunocompromised condition of these patients due to neoplastic treatment. Furthermore, the large exposure of tissues during this type of surgery and the dissection across vascular distributions also contributes to the high risk of infection. The authors reviewed the literature discussing the incidence of infections of tumor prosthesis implanted following resection of bone tumors, taking into account the different sites of implantation. In the English literature, the highest risk of infection which led to limb amputation was observed after proximal tibia resection and this difference was considered to be due to the poor condition of soft tissue and also after pelvic resection due to huge dead space after sarcoma resection not filled by implant. Independent of the location, the management of infected prosthesis is similar. That is, after one or more attempts at debridement and antibiotic therapy, it consists of implant removal and insertion of a new implant in a one- or two-stage procedure, with a decreased risk of failure with the two-stage procedure.

LUTEOLIN AND THIOSALICYLATE INHIBIT HgCl₂ AND THIMEROSAL-INDUCED VEGF RELEASE FROM HUMAN MAST CELLS

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HgCl₂ is a known environmental neurotoxin, but is also used as preservative in vaccines as thimerosal containing ethyl mercury covalently linked to thiosalicylate. We recently reported that mercury chloride (HgCl₂) can stimulate human mast cells to release vascular endothelial growth factor (VEGF), which is also vasoactive and pro-inflammatory. Here we show that thimerosal induces significant VEGF release from human leukemic cultured LAD2 mast cells (at 1 μM 326±12 pg/10⁶ cells and 335.5±12 pg/10⁶ cells at 10 μM) compared to control cells (242±21 pg/10⁶ cells, n=5, p<0.05); this effect is weaker than that induced by HgCl₂ at 10 μM (448±14 pg/10⁶ cells) (n=3, p<0.05). In view of this finding, we hypothesize that the thiosalicylate component of thimerosal may have an inhibitory effect on VEGF release. Thimerosal (10 μM) added together with the peptide Substance P (SP) at 2 μM, used as a positive control, reduced VEGF release by 90%. Methyl thiosalicylate (1 or 10 μM) added with either SP or HgCl₂ (10 μM) inhibited VEGF release by 100%, while sodium salicylate or ibuprofen had no effect. Pretreatment for 10 min with the flavonoid luteolin (0.1 mM) before HgCl₂ or thimerosal completely blocked their effect. Luteolin and methyl thiosalicylate may be useful in preventing mercury-induced toxicity.
MONOMERIC ALLERGOID INTRAGASTRIC ADMINISTRATION INDUCES LOCAL AND SYSTEMIC TOLEROGENTIC RESPONSE INVOLVING IL-10-PRODUCING CD4\(^+\)CD25\(^+\) T REGULATORY CELLS IN MICE

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The efficacy of sublingual immunotherapy, at present one of the treatments of choice for respiratory allergy, relies on the tolerance induced by oral mucosa-associated immune system; however, the gut-associated lymphoid tissue (GALT: Peyer’s patches and isolated lymphoid follicles) and mesenteric lymph nodes could also be involved, being stimulated by the ingested part of the allergen extract. The aim of the present study is to assess whether the exposure of the allergen exclusively to the GALT induces a tolerogenic response. To this purpose, mice were sensitized with ovalbumin or Par j 1 allergens. The corresponding gastric-resistant monomeric allergoids were then administered via orogastric gavage. After treatment, all mice were tested for: serum IgE, \textit{in vitro} Th1 and Th2 cytokine release by allergen-stimulated peripheral blood lymphocytes, CD4\(^+\)CD25\(^+\) and CD4\(^+\)CD25\(^+\)IL-10\(^+\) T cells in Peyer’s patches, mesenteric lymph nodes and spleen. Compared to the control, sensitized groups showed higher levels of serum IgE, lower frequency of CD4\(^+\)CD25\(^+\)IL-10\(^+\) T cells, at all sites, and higher amounts of \textit{in vitro}-released IL-4, IL-6 and TNF-\(\alpha\). Compared to the sensitized groups, higher frequency of CD4\(^+\)CD25\(^+\)IL-10\(^+\) T cells was observed in the spleen of both Par-j 1 and OVA sensitized/treated groups and, only for ovalbumin-treated mice, in the Peyer’s patches and mesenteric lymph nodes, IgE and \textit{in vitro} cytokines were significantly lower and equivalent to the control group. The results give the first evidence that the intragastric-restricted administration of gastric-resistant allergens restores local and peripheral tolerance in allergen-sensitized mice.
GW0742, A HIGH AFFINITY PPAR-β/δ AGONIST REDUCES LUNG INFLAMMATION INDUCED BY BLEOMYCIN INSTILLATION IN MICE

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Peroxisome Proliferator-Activated Receptor β/δ belongs to a family of ligand-activated transcription factors. Recent data have clarified its metabolic roles and enhanced the potential role of this receptor as a pharmacological target. Moreover, although its role in acute inflammation remains unclear, being the nuclear receptor PPAR β/δ widely expressed in many tissues, including the vascular endothelium, we assume that the infiltration of PMNs into tissues, a prominent feature in inflammation, may also be related to PPAR β/δ. Mice subjected to intratracheal instillation of bleomycin (BLEO, 1 mg/kg), a glycopeptide produced by the bacterium Streptomyces verticillus, develop lung inflammation and injury characterized by a significant neutrophil infiltration and tissue oedema. Therefore, the aim of this study is to investigate the effects of GW0742, a synthetic high affinity PPAR β/δ agonist, and its possible role in preventing the advance of inflammatory and apoptotic processes induced by bleomycin, that long-term leads to the appearance of pulmonary fibrosis. Our data showed that GW0742-treatment (0.3 mg/Kg, 10% DMSO, i.p.) has therapeutic effects on pulmonary damage, decreasing many inflammatory and apoptotic parameters detected by measurement of: 1) cytokine production; 2) leukocyte accumulation, indirectly measured as decrease of myeloperoxidase (MPO) activity; 3) IκBα degradation and NF-κB nuclear translocation; 4) ERK phosphorylation; 5) stress oxidative by NO formation due to iNOS expression; 6) nitrotyrosine and PAR localization; 7) the degree of apoptosis, evaluated by Bax and Bcl-2 balance, FAS ligand expression and TUNEL staining. Taken together, our results clearly show that GW0742 reduces the lung injury and inflammation due to the intratracheal BLEO-instillation in mice.
CONTROVERSIAL ROLE OF ANTIBODIES AGAINST LINEAR EPITOPES
OF DESMOGLEIN 3 IN PEMPHIGUS VULGARIS, AS REVEALED BY
SEMIQUANTITATIVE LIVING CELL IMMUNOFLUORESCENCE MICROSCOPY AND
IN-CELL ELISA

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A novel explanation of pemphigus vulgaris (PV) pathogenesis suggests that serum autoantibodies
may affect desmoglein 3 (Dsg3)-mediated adhesion by triggering depletion of Dsg3 from desmosomes.
Furthermore, abrogation of Dsg3 from the cell seems to depend on anti-Dsg3 pemphigus IgG. In this
study we sought to gain more insights into the role of PV IgG recognizing non-conformational epitopes
of Dsg3 (anti-Dsg3-L IgG) by semi-quantitative living cell immunofluorescence (LCIF) microscopy, in-cell
ELISA and morphometric analysis of acantholysis. Our data demonstrate that PV serum and PV IgG can
induce acantholysis and reduce the total amount of Dsg3 in cultured keratinocytes, whereas anti-Dsg3-L
IgG fail to do so when administered at concentrations comparable to those present in pathogenic PV sera.
However, the Dsg3-depleting activity of such polyclonal anti-Dsg3 IgG was acquired when used at 1 μg/ml.
Interestingly, both PV sera and IgG, including anti-Dsg3-L IgG, caused early depletion of surface Dsg3
while slightly affecting the total cell content of Dsg3 until late acantholysis. This raises a possibility that
depletion of Dsg3 from cell membrane and reduction of the total cellular levels of Dsg3 represent distinct
phenomena in PV acantholysis. Taken together, our data demonstrate that anti-Dsg3 PV IgG against
linear epitopes of Dsg3 can induce acantholytic changes of keratinocytes in a dose- and time-dependent
manner. Specifically, both morphological and biochemical changes suggestive of acantholysis are seen only
at high IgG concentrations. We conclude that anti-Dsg3L IgG play a minor role in experimental PV under
physiologic conditions.

EFFECTS OF TNF-α AND IL-1β ON THE ACTIVATION OF GENES RELATED TO
INFLAMMATORY, IMMUNE RESPONSES AND CELL DEATH IN IMMORTALIZED
HUMAN HaCat KERATINOCYTES

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The present experiments were designed to characterize by microarray analysis the transcriptional
responses of human keratinocytes (HaCat) to TNF-α and IL-1β, given alone or in combination, in order to
better understand the mechanisms underlying inflammatory, immune responses and cell death in which
both cytokines play a pathophysiological role. Significant differences in the percentage and quality of
genes dysregulated by TNF-α and IL-1β were shown. Both cytokines activated a series of genes involved
in inflammatory, immune response as well as in cell death. In our experimental conditions, TNF-α,
in contrast to IL-1β, did not induce a significant level of apoptosis in keratinocytes. However, given
together both cytokines produced a significant decrease in apoptotic cells and synergistic transcriptional
response which was due to the activation of several specific genes occurring after application of each
cytokine. TNF-α and IL-1β evoked apoptotic effect and transcriptional responses were linked to the
stimulation of their specific receptors since a pre-treatment with monoclonal antibodies vs TNF-α and/or
IL-1β receptors was able to significantly reduce them.
CAFETERIA DIET INCREASES PROSTAGLANDIN E\(_2\) LEVELS IN RAT PROSTATE, KIDNEY AND TESTIS

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Nutrient composition, particularly the omega-6/omega-3 polyunsaturated fatty acids ratio, may differently affect inflammatory mediators production in tissues, which could be causally related to increased cancer incidence in obesity. We evaluated prostaglandin E\(_2\) levels in male Wistar rat prostate, kidney and testicle tissues after 15 days of either a high fat, cafeteria-style diet (5.50 Kcal/g, 30% calories from fat, omega-6/omega-3 ratio 2.33) or a standard laboratory chow diet (3.35 Kcal/g, 3% calories from fat, omega-6/omega-3 ratio 0.56). In the cafeteria diet compared to standard laboratory diet rats, we found both an increase in weight gain and increased prostaglandin E\(_2\) (PGE\(_2\)) levels in prostate, kidney and testicle tissues. The increased levels of PGE\(_2\) induced by the cafeteria diet could drive an inflammatory process leading to increased incidence of prostate, kidney and testicular cancer in overweight patients.

DENDRITIC CELL DIFFERENTIATION BLOCKED BY PRIMARY EFFUSION LYMPHOMA-RELEASED FACTORS IS PARTIALLY RESTORED BY INHIBITION OF P38 MAPK

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To better understand the molecular mechanisms underlying the dendritic cell (DC) defects in cancer, we analyzed which signaling pathway is implicated in the abnormal monocyte differentiation into DC determined by the presence of Primary effusion lymphoma (PEL) released factors. Our results indicate that the DC, obtained in this condition, together with phenotypic abnormalities and reduced allostimulatory function, showed hyperphosphorylation of signal transducer and activator of transcription 3 (STAT3) and p38 mitogen-activated protein kinase (MAPK) molecules, in comparison to the DC differentiated in the absence of PEL-released factors. The inhibition of p38 MAPK but not of STAT3 phosphorylation, with specific inhibitors, was able to revert the effect of the PEL-released factors on the DC phenotype. This study suggests that p38 MAPK signaling pathway is an important contributor to the abnormal differentiation of DC in PEL.
ETHYL PYRUVATE THERAPY ATTENUATES EXPERIMENTAL SEVERE ARTHRITIS CAUSED BY TYPE II COLLAGEN (CII) IN THE MOUSE (CIA)

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This study tested the hypothesis that ethyl pyruvate (EP), a simple aliphatic ester with anti-inflammatory effects, can reduce type II collagen-induced mouse arthritis (CIA). DBA/1J mice were used for the study, developing erosive hind paw arthritis when immunized with CII in an emulsion in complete Freund’s adjuvant (CFA). The incidence of CIA was 100% by day 28 in the CII-challenged mice, and the severity of CIA progressed over a 35-day period with radiographic evaluation revealing focal resorption of bone. The histopathology of CIA included erosion of the cartilage at the joint margins. EP-treatment (40 mg/kg/day i.p.) starting at the onset of arthritis (day 25) ameliorated the clinical signs at days 26-35 and improved histological status in the joint and paw. Immunohistochemical analysis for nitrotyrosine, poly (ADP-ribose) (PAR), inducible nitric oxide synthase (iNOS) revealed a positive staining in inflamed joints from mice subjected to CIA, while no staining was observed for HO-1 and Nrf-2 in the same group. The degree of staining for nitrotyrosine, PAR, iNOS, was significantly reduced in CII-challenged mice treated with the EP. Immunohistochemical staining for HO-1 and Nrf-2 was observed instead, in joints obtained from the EP-treated group. Plasma levels of TNF-a, IL-6 and the joint tissue levels of macrophage inflammatory protein (MIP)-1α and MIP-2 were also significantly reduced by EP treatment. Thirty-five days after immunization, EP-treatment significantly increased plasma levels of IL-10. These data demonstrate that EP treatment exerts an anti-inflammatory effect during chronic inflammation and is able to ameliorate the tissue damage associated with CIA.
REDUCTIVE ALTERATION OF THE REGULATORY FUNCTION OF THE CD4+CD25+ T CELL FRACTION IN SILICOSIS PATIENTS

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Causal links have been documented between silica and rheumatoid arthritis, lupus erythematosus, systemic sclerosis and glomerulonephritis. Two different effects of silica have been suggested, an enhanced inflammatory response in the pulmonary region (e.g. activation of alveolar macrophages) and dysregulation of autoimmunity. Based on our previous reports showing in vitro activation of peripheral T cells by silica and reduced regulatory function of the peripheral CD4+CD25+ fraction in which FoxP3+ regulatory T cells (Treg) are located, reconstitution of the CD4+CD25+ fraction in silicosis patients (SILs) was investigated. Since T cells in peripheral CD4+CD25+ and CD4+CD25− (effector T cells; Teff) fractions from SILs showed higher expression of pd-1 (a marker gene for T cell activation) in comparison to that of healthy donors (HDs), chronic T cell activation was considered to have occurred in SILs. In this study, a higher expression of the CD95/Fas molecule in Treg was recorded from silicosis patients (SILs) compared to healthy donors (HDs), and excess loss of FoxP3+ Treg in freshly isolated peripheral blood mononuclear cells (PBMCs) from SILs relative to HDs was demonstrated when these cells were cultured with silica ex vivo, whereas CD25+ cells were not reduced due to contamination of activated Teff in the CD4+CD25+ fraction. The activation of both Teff and Treg results in reconstitution of the peripheral CD4+ CD25+ fraction, loss of Treg and contamination of activated Teff, resulting in reduction of the number and function of Treg. These results contribute to our understanding of the development of autoimmune diseases found in SILs.
RESPONSE OF CRYPT PANETH CELLS IN THE SMALL INTESTINE FOLLOWING TOTAL-BODY $\gamma$-IRRADIATION

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Ionizing irradiation causes damage and functional failure of irradiation-sensitive systems and tissues such as small intestine. The molecular mechanisms underlying inflammatory and adaptive responses to acute irradiation damage are poorly understood. Using a mouse model of total-body $\gamma$-irradiation, we assessed the irradiation response of crypt host-defense Paneth cells by measuring $\alpha$-defensin 4 (AD4) expression and correlated the gathered data with activation of the caspase-1/IL-1$\beta$ inflammatory signaling cascade. The irradiation injury was produced in CD2F1 mice exposed to 9.25 Gy $\gamma$-radiation. This dose resulted in 85-100% mortality at the 15th day post-irradiation. Small intestine tissue samples were collected at the 7th day post-irradiation. Assessment of irradiation-associated pro-inflammatory alterations in small intestine tissue and expression of AD4 in Paneth cells was conducted using confocal immunofluorescence imaging, transmission electron microscopy (TEM), light microscopy, and immunoblotting techniques. The small intestine analysis revealed an increase in the precursor form of IL-1$\beta$, the activated form of IL-1$\beta$, and the activated form of caspase-1 (p10 CASP-1) at the 7th day post-irradiation. Immunoprecipitation analysis showed increased interaction between IL-1$\beta$ and p10 CASP-1 after irradiation. This effect was observed in the irradiated small intestine and CD15-positive Paneth cells using confocal imaging techniques. The pro-inflammatory alterations in Paneth cells were accompanied by increases in AD4 mRNA and its 8 kD peptide product. Paneth cell secretory activity was observed at the sites of bacterial translocation in the crypt lumens. These data suggest that Paneth cells can contribute to small intestine inflammatory remodeling during the post-irradiation period.
EFFECTS OF TOLUIDINE BLUE-MEDIATED PHOTODYNAMIC THERAPY ON PERIOPATHOGENS AND PERIODONTAL BIOFILM: IN VITRO EVALUATION

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Photodynamic therapy (PDT) is a selective modality of killing targeted cells, mostly known for its application in neoplasms. PDT can be considered to be an alternative method for the elimination of periodontal bacteria from the pocket without harms for the resident tissues. Therefore, PDT may replace systemic antibiotics and enhance the effect of mechanical treatments of periodontal defects. This effort focused on the in vitro sensitization of periopathogens (Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum and Prevotella intermedia) Toluidine Blue mediated and on the use of a Diod Laser emitting source. The objective of this research was to evaluate the bactericidal in vitro effect of laser diodes 830 nm (as the light source) after photosensitization with Toluidine Blue (TBO) on the following periopathogenic bacteria: Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum and Prevotella intermedia. After evaluating the effect on the single bacterial strain, the ability of Diode Laser to disrupt the structure of biofilms produced by A. actinomycetemcomitans after photosensitization with TBO was also analyzed. The study suggests that the association of TBO and diode laser light 830 nm is effective for the killing of bacteria strains and determines the photoinactivation of Aggregatibacter biofilms. In summary, photodynamic therapy has effectively shown its capabilities and, therefore, it can be considered a valid alternative approach to antimicrobial therapy of periodontitis.
DEVELOPMENT AND PRELIMINARY VALIDATION OF A DIAGNOSTIC SCORE FOR IDENTIFYING PATIENTS AFFECTED WITH ADULT-ONSET AUTOINFLAMMATORY DISORDERS

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To date, the rate of detection of autoinflammatory gene mutations in patients suspected of having an autoinflammatory disorder is very low. However, most of these data refer to pediatric populations. The relative rarity and lack of information on adult-onset autoinflammatory diseases make it likely that mutations will be found in an even smaller percentage of cases. Our aim was to develop and validate a set of variables for predicting the risk that a given adult patient presenting with recurrent fever episodes carries mutations in the \textit{MEFV} or \textit{TNFRSF1A} genes, in order to increase the probability of obtaining positive results on genetic testing. One hundred and ten consecutive patients with a clinical history of periodic fever attacks were screened for mutations in the \textit{TNFRSF1A} and the \textit{MEFV} genes. The mean age at disease onset was 27.85 years. Detailed information about each patient’s family history, personal history, and clinical manifestations were retrospectively collected. A diagnostic score was constructed based on univariate and multivariate analysis in a randomly-selected dataset (training set; n=40). The score was validated on an independent set of the remaining patients (validation set; n=70). Age at onset (odds ratio [OR] 0.958, \(P =0.050\)), positive family history of recurrent fever episodes (OR 5.738, \(P = 0.006\)), thoracic pain (OR 7.390, \(P = 0.002\)), abdominal pain (OR 2.853, \(P = 0.038\)) and skin involvement (OR 8.241, \(P = 0.003\)) were independently correlated with a positive genetic test result. A diagnostic score was calculated using the linear combination of the estimated coefficients of the logistic model (cut off equal to 0.24) revealing high sensitivity (0.94), high specificity (0.94) and high accuracy (0.94). We have identified variables that appear to be strongly related to the probability of detecting gene mutations in \textit{MEF} and \textit{TNFRSF1A} in adults, thus improving the evaluation of patients with suspected autoinflammatory disorders.
PSORIASIS RELAPSE EVALUATION WITH WEEK-END CYCLOSPORINE A TREATMENT: RESULTS OF A RANDOMIZED, DOUBLE-BLIND, MULTICENTER STUDY

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Cyclosporine A (CsA) effectively controls psoriasis, however, its long-term continuous use is not recommended. This study aims to evaluate the efficacy and tolerability of week-end CsA microemulsion for the reduction of relapse rate in patients with chronic plaque psoriasis who had achieved clinical remission following continuous CsA therapy. The PREWENT (Psoriasis Relapse Evaluation with Week-End Neoral Treatment) study was a 24-week, randomized, double-blind, multicenter study, carried out in 22 Italian hospital or university Dermatology units. CsA was discontinued for 8 days previous to the patients being randomized to oral CsA 5 mg/kg/day or placebo for two consecutive days/week, for a total period of 24 weeks. The primary endpoint was clinical success rate at week 24, defined as the proportion of patients with no clinical worsening (no relapse or a Psoriasis Area and Severity Index [PASI] <75% of pre-treatment PASI). A total of 162 patients were randomized to CsA and 81 to placebo. Clinical success rates at 24 weeks were 66.9% and 53.2% with CsA and placebo, respectively (p = 0.072). Time to first relapse was significantly prolonged with CsA versus placebo (p = 0.023), and PASI was significantly lower from weeks 4 to 16 in CsA recipients. In patients with moderate-severe psoriasis, the clinical success rate was significantly increased with CsA compared to placebo (69.9% vs 46.3%; p = 0.011), and significantly lower increases in PASI were observed from week 4 to week 24 (p < 0.05 vs placebo). CsA was well tolerated, with no differences in mean blood creatinine or blood pressure between CsA and placebo recipients. However, the high withdrawal rate (22.2% of randomized patients), which was not related to side effects, may have led to an overestimation of efficacy, but the study had a good statistical power (88% greater than that observed in similar studies, i.e. 80%). Week-end CsA administration was shown to prolong safely and effectively the time to first relapse in psoriasis patients.
DEXAMETHASONE AFFECTS FAS- AND SERUM DEPRIVATION-INDUCED CELL DEATH OF HUMAN OSTEOBLASTIC CELLS THROUGH SURVIVIN REGULATION

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Glucocorticoid-induced bone loss is the most prevalent form of secondary osteoporosis. Such loss could be due to the alteration of osteoclast and osteoblast lifespan through regulated apoptosis. The current study investigated the effect of dexamethasone on Fas- and starvation-induced apoptosis of mature osteoblasts and their precursors. Using the human osteoblastic hFOB1.19 and the MG63 osteosarcoma cell lines, we found that sub-lethal doses of dexamethasone act on pre-osteoblasts but not on mature cells by increasing their susceptibility to apoptosis. Apoptosis occurs in a caspase-dependent manner as both DNA fragmentation and mitochondrial transmembrane potential dissipation (ΔΨ\(_m\)) are inhibited by the pan-caspase inhibitor zVAD. The increased susceptibility of osteoblast precursors to apoptosis could be due to dexamethasone-mediated down-regulation of survivin expression. Dexamethasone can up-regulate survivin, and to a lesser extent Bcl-2, in mature cells but not in pre-osteoblasts. In addition, it can induce FLIP over-expression in osteosarcoma cells. All these effects are inhibited by the glucocorticoid antagonist RU486, indicating that dexamethasone action is specific and, furthermore, that it depends on glucocorticoid receptor. Finally, we have found that survivin and Bcl-2 are essential for pre- and mature osteoblast survival as their silencing is sufficient to induce spontaneous apoptosis in both cell types. In conclusion, our data outline a new molecular mechanism of glucocorticoid-mediated bone loss due to the enhanced apoptosis of precursors compared to mature osteoblasts. Furthermore, the data suggest a mechanism of dexamethasone-induced resistance of osteosarcoma cells to Fas- and stress-induced apoptosis.
INHIBITION OF HSV-1 REPLICATION BY LASER DIODE-IRRADIATION: POSSIBLE MECHANISM OF ACTION

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Herpes labialis are the most frequent clinical manifestations of HSV-1 infection. Epithelial cells are able to respond to HSV-1 presence inducing the expression of IL-6, IL-1, TNF-α and IL-8. These proinflammatory cytokines have a function in the acute-phase response mediation, chemotaxis, inflammatory cell activation and antigen-presenting cells. In the human epithelial cell models, it has been demonstrated that, after an early induction of proinflammatory host response, HSV-1 down-modulates the proinflammatory cytokine production through the accumulation of two viral proteins, ICP4 and ICP27, whose transcription is induced by tegument protein VP16. These viral proteins, through the decreasing of stabilizing the mRNAs of proinflammatory genes, delay cytokine production to an extent that allows the virus to replicate. Moreover, viral transactivating proteins, ICP-0 and VP-16 induce IL-10 expression. The conventional treatment of herpes labialis involves the topical and systemic use of antiviral drugs but it is necessary to find new therapies that can act in a selective and non-cytotoxic manner in viral infection. Laser diode therapy has been considered as a non-invasive alternative treatment to the conventional treatment of herpes labialis in pain therapy, in modulation of inflammation and in wound healing. This study aims to report a possible mechanism of action of laser diode irradiation in prevention and reduction of severity of labial manifestations of herpes labialis virus. We investigated, in an in vitro model of epithelial cells HaCat, the laser-effect on HSV-1 replication and we evaluated the modulation of expression of certain proinflammatory cytokines (TNF-α, IL-1β and IL-6), antimicrobial peptide HBD2, chemokine IL-8 and the immunosuppressive cytokine, IL-10. Our results lead us to hypothesize that LD-irradiation acts in the final stage of HSV-1 replication by limiting viral spread from cell to cell and that laser therapy acts also on the host immune response unblocking the suppression of proinflammatory mediators induced by accumulation of progeny virus in infected epithelial cells.
BIOAVAILABILITY OF SANDIMMUN® VERSUS SANDIMMUN NEORAL®: A META-ANALYSIS OF PUBLISHED STUDIES

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For the past 25 years, cyclosporine A (CyA) has played a pivotal role in transplant immunosuppressant therapy. From the availability of the 2 primary marketed formulations (Sandimmun® and Sandimmun Neoral®, Novartis), confusion has existed with regard to whether these two formulations are bioequivalent. Due to the underlying clinical relevance of this information, we therefore conducted a meta-analysis of all available comparative pharmacokinetic studies to assess whether the two different CyA formulations, Sandimmun® and Sandimmun Neoral®, can be considered bioequivalent. All clinical studies that compared the bioavailability of the 2 formulations in organ transplant recipients were considered for analysis. We searched computerised databases (Embase/Excerpta Medica and Medline/PubMed) from their inception to May 2010. Only studies with AUC values determined at 12 hours were considered for analysis. Relative bioavailability was calculated with 90% confidence intervals (CI) for Sandimmun® (test substance) versus Sandimmun Neoral® (reference substance) according to Schuirmann’s Two One-Sided Tests Procedure and the Classical Shortest CI. Homogeneity of data was tested using the \( \chi^2 \) test. Fifteen studies were considered for meta-analysis and none of these studies reported AUC values in the 80%-125% range required for the bioequivalence of two formulations. The overall bioavailability for Sandimmun® versus the microemulsion formulation Sandimmun Neoral® was 76%, with upper CI limits lower than 80% in some cases. Mean AUC values for Sandimmun® were significantly lower than those for Sandimmun Neoral® (\( p<0.01 \)). This study demonstrates that the 2 main cyclosporine formulations, Sandimmun® and Sandimmun Neoral®, cannot be considered bioequivalent.

BOSENTAN TREATMENT FOR RAYNAUD’S PHENOMENON AND SKIN FIBROSIS IN PATIENTS WITH SYSTEMIC SCLEROSIS AND PULMONARY ARTERIAL HYPERTENSION: AN OPEN-LABEL, OBSERVATIONAL, RETROSPECTIVE STUDY


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Raynaud’s phenomenon (RP) and cutaneous fibrosis are the distinctive manifestations of scleroderma, in which Endothelin-1 plays a fundamental pathogenetic role. Bosentan, an Endothelin-1 receptor antagonist used for the treatment of pulmonary arterial hypertension, retards the beginning of new sclerodermic digital ulcers (DU). This open-label, observational, retrospective study verified the effect of Bosentan on RP and skin fibrosis in sclerodermic outpatients affected by pulmonary arterial hypertension without DU. Fourteen subjects (13 women, 1 man; mean age 60 ± 7.5 years; ten with limited and four with diffuse scleroderma) were observed at baseline (T0) and after four (T1), twelve (T2), twenty-four (T3) and forty-eight (T4) weeks during treatment with Bosentan. They were evaluated for daily quantity and duration of RP attacks and skin thickness (using modified Rodnan total skin score, MRSS). Videocapillaroscopic evaluation was performed at T0 and T4. Bosentan decreased significantly the number and duration of RP attacks, beginning at T2 (\( p<0.05 \)). Videocapillaroscopy showed significant improvement of microcirculatory patterns at T4 (\( p<0.05 \)). MRSS decreased throughout the study, reaching the statistical significance at T3 and T4 (\( p<0.01 \)) in the whole cohort. The present data suggest that Bosentan is effective in stabilizing the microcirculation involvement and in improving skin fibrosis irrespective of scleroderma patterns.
C-REACTIVE PROTEIN AND MARKERS FOR THROMBOPHILIA IN PATIENTS WITH CHRONIC PLAQUE PSORIASIS

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Chronic plaque psoriasis is associated to an increased risk of cardiovascular events. The aim of our study is to test patients with psoriasis for common markers of acquired and inherited thrombophilia. A cross-sectional study on 172 patients with psoriasis and 198 controls was carried out. The plasma levels of coagulation protein C, coagulation protein S, homocysteine, folic acid, C-reactive protein (CRP) and fibrinogen as well as activated protein C resistance and antithrombin III activity, were measured. CRP and homocysteine levels were higher in patients with psoriasis than in controls (5.9 ± 7.1 vs 3.1 ± 2.4 mg/L, p=0.0003 and 16.3 ± 12.8 vs 10.4 ± 4.6 umol/L, p=0.0001; mean ± SD) whereas folic acid was lower in psoriatic patients compared to controls (4.3 ± 7.2 vs 12.6 ± 7.9 p=0.006). Levels of coagulation protein C, coagulation protein S, fibrinogen as well as activated protein C resistance, antithrombin III activity were within normal ranges both in cases and controls. In a multivariate regression analysis, psoriasis severity was an independent predictor of higher CRP. In conclusion, high levels of serum CRP and homocysteine were found in patients with psoriasis, related to the severity of the disease. These data suggest that the increased risk of thrombotic cardiovascular events observed in psoriasis patients should be ascribed to an acquired rather than inherited thrombophilic status.

THE PRESENCE OF NON-SEGMENTAL VITILIGO MODIFIES INTRACELLULAR CYTOKINE SUBSETS IN PATIENTS WITH CHRONIC LYMPHOCYTIC THYROIDITIS

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Chronic lymphocytic thyroiditis and vitiligo often occur in association and seem to be characterized by a prevalent Th1-driven autoimmune process. The aim of this study is to analyze selected intracellular Th1 and Th2 cytokines in patients with Hashimoto’s thyroiditis when associated with non-segmental vitiligo. We analyzed intracellular interleukin-2, interferon-γ (Th1) and interleukin-4 (Th2), in peripheral blood lymphocytes of 23 patients with isolated Hashimoto’s thyroiditis (group A) and of 11 patients with Hashimoto’s thyroiditis associated with non-segmental vitiligo (group B). Peripheral blood lymphocytes were stimulated and incubated with specific monoclonal antibodies. Intracellular cytokines were assayed by flow cytometric analysis. Interleukin-2 and interferon-γ positive cells were increased in almost all patients but the median values were similar in patients with isolated Hashimoto’s thyroiditis and in those with concurrent vitiligo. In contrast, the number of patients with increased interleukin-4 positive cells was higher in patients with thyroiditis and vitiligo (9/11) than in those with isolated thyroiditis (2/23; p=0.0001). The median values of IL-4 positive cells in the two groups confirmed this difference (A: 5.8%, vs B: 20.6%; p=0.0011). Increased interleukin-4 positive lymphocytes characterize Hashimoto’s thyroiditis when associated with non-segmental vitiligo, suggesting a modified balance from highly prevalent Th1 to mixed Th1/Th2 subset.
United airway disease (UAD) concept proposed that asthma and rhinitis are both different clinical manifestation of a single inflammatory process. The aim of this study is to assess in upper and lower airways the level of inflammation and oxidative stress and to investigate the relationship between biomarkers in persistent allergic rhinitis (PER) and in concomitant asthma with PER. By a cross-sectional study we measured oral and nasal (FE\textsubscript{NO}) and oral and nasal EBC 8-isoprostane, LTB\textsubscript{4} and PGE\textsubscript{2} in children with PER (n=14) and with PER and concomitant intermittent asthma (IA; n=25), mild persistent asthma (mA; n=28), moderate persistent asthma (MA; n=13) and in Healthy Controls (HCs; n=13). Oral and nasal FE\textsubscript{NO} concentrations were increased in children with PER, IA, mA and MA when compared with HCs. Nasal 8-isoprostane was higher in EBC of children with PER and asthma than in HCs. Oral and nasal LTB\textsubscript{4} were higher in EBC of children with PER and mA than in HCs. Oral and nasal PGE\textsubscript{2} concentrations were higher in EBC of children with PER than in HCs. Positive correlations between oral and nasal biomarkers were found in IA for LTB4 and PGE2, in mA for FE\textsubscript{NO}, 8-isoprostane, LTB\textsubscript{4} and PGE\textsubscript{2}, and in MA for PGE\textsubscript{2}. No correlations were observed in children with PER and HCs. Our results suggest that non-invasive markers of inflammation and oxidative stress might be useful to study the relationships between oral and nasal compartments in allergic children with PER and concomitant asthma with the aim of defining the UAD.
THE CLINICAL IMPACT OF A CARDIOLOGIC FOLLOW-UP IN BREAST CANCER SURVIVORS: AN OBSERVATIONAL STUDY


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Anthracycline-containing chemotherapy (A-CHT) can induce late cardiotoxicity adding a considerable burden to cardiovascular risk. Irradiation of left breast cancer has also been associated to an increased risk of cardiovascular disease. The aim of this observational study is to prove the usefulness of an accurate cardiovascular evaluation in left breast cancer survivors treated with radiotherapy (RT) and A-CHT. Patients with left breast cancer, on follow-up after treatment with A-CHT plus RT in an adjuvant setting, were eligible for this observational study. Patients underwent cardiovascular assessment with myocardial perfusion imaging. Thirty patients were enrolled in the study: mean age at diagnosis 55.8 years; stage: I/III; Er and/or pgR status: positive in 24/30 pts; 3 patients in pre-menopausal status. Twenty-two patients (73.3%) had normal perfusion imaging, 1 patient (3.3%) had a fixed myocardial perfusion defect, 7 patients (23.3%) had reversible myocardial perfusion defects; 1 patient (3%) with normal perfusion scan showed depressed rest and stress LVEF. Only 1 patient had a large defect and underwent coronary angiography and percutaneous coronary intervention. Five patients with small defect showed normal coronary arteries at Multislice Computed Tomography. Cardiovascular follow-up may reveal signs of A-CHT or RT-induced cardiotoxicity. A stress test combined with MPI- and GATED-derived data of ventricular systolic performance after stress can give information on the coronary reserve and the contractile reserve and allow early appropriate treatment.
MICRON RNA EXPRESSION PROFILING OF ORAL CARCINOMA IDENTIFIES NEW MARKERS OF TUMOR PROGRESSION


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Oral squamous cell carcinoma, the most frequently occurring malignant head and neck tumour, generally exhibits poor prognosis and metastases are the main cause of death. The discovery of reliable prognostic indicators of tumour progression could greatly improve clinical practice. MicroRNAs are involved in the regulation of basic cellular processes such as cell proliferation, differentiation, and apoptosis. Since miRNAs have been shown to be abnormally expressed in different tumours their importance as potential cancer prognostic indicators is increasing. To define the role of miRNA in OSCC tumours we investigated the expression profile of 15 OSCC (8 without metastasis and 7 with lymph node metastasis) using microarray analysis. Thirteen miRNA were significantly overexpressed (miR-489, miR-129, miR-23a, miR-23b, miR-92, miR-25, miR-210, miR-212, miR-515, miR-146b, miR-21, miR-338) and 6 miRNA were underexpressed (miR-520h, miR-197, miR-378, miR-135b, miR-224, miR-34a) in oral tumours. Underexpression of mir-155, let-7i, mir-146a was found to characterize progression to metastastatic tumours. Further investigations will elucidate whether differentially expressed miRNAs will help to better classify OSCCs, thus improving diagnoses and patient care.

ADJUVANT EFFECT OF A PROBIOTIC FERMENTED MILK IN THE PROTECTION AGAINST SALMONELLA ENTERITIDIS SEROVAR TYPHIMURIUM INFECTION: MECHANISMS INVOLVED

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Probiotics may offer protection against Salmonella enteritidis serovar Typhimurium infection via different mechanisms. The aim of this study is to investigate, using mouse models, the effect of the administration of fermented milk containing the probiotic bacteria L. casei DN-114 001 in the protection against Salmonella enteritidis serovar Typhimurium when this product is administered continuously before and after infection or only post-infection. The adjuvant effect of this probiotic fermented milk (PFM) against S. Typhimurium was also evaluated in newborn mice, whose mothers received the PFM during the suckling period or their offspring after weaning. The results obtained showed that PFM administration after salmonella infection was useful to decrease the severity of the infection. The best effect was obtained with continuous PFM administration. In the newborn mice model, PFM administration to the newborn mice after weaning showed the best effect against the pathogen. PFM administration to the mother during the suckling period was beneficial against this enterophatogen when their offspring did not receive probiotics after weaning. Continuous PFM administration to adult mice (before and after infection) was important to maintain the intestinal barrier and the immune surveillance in optimal conditions to diminish the pathway of entrance of salmonella and the spread of this pathogen to deeper tissues. In the newborn mice model, it was observed that PFM administration to the offspring after weaning or their mother during the suckling period had a protective effect against salmonella infection, however, in the mice from mothers that received PFM during nursing which were fed with PFM after weaning, we found a down regulated immune maturity that was not protective against this infection.
CHLAMYDOPHILA PNEUMONIAE INFECTION IN PATIENTS UNDERGOING CAROTID ARTERY STENT

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Although several reports have correlated Chlamydia pneumoniae (CP) infection with carotid endarterectomy and coronary stent, no data have been reported on the potential relationship between this pathogen and carotid artery stenting (CAS). Hence, we evaluated 47 subjects, 27 symptomatic and 20 asymptomatic, before CAS intervention and during the follow up, for the presence of CP DNA and anti-CP antibodies, including chlamydial HSP60 (Cp-HSP60). Before stent placement, CP DNA was detected exclusively in symptomatic patients, all of whom were also positive for CP IgG and IgA and 85.7% of them also had Cp-HSP60 antibodies. At the follow-up, all CP DNA positive and 11 out of the 13 symptomatic patients with Cp-HSP60 antibodies became negatives. In contrast, no change was observed for CP-IgA antibodies. Despite the small number of patients, the present study advocates an important role of CP infection in symptomatic patients with carotid artery disease. Our findings also suggest that stent placement and/or therapy might have a role in favouring resolution of inflammation, though not affecting persistence of CP infection.

STREPTOCOCCUS MUTANS AND STREPTOCOCCUS SOBRINUS ARE ABLE TO ADHERE AND INVADE HUMAN GINGIVAL FIBROBLAST CELL LINE

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Streptococcus mutans and Streptococcus sobrinus, the principal etiologic agents of caries decay of teeth, are generally acquired in oral cavity at the moment of tooth eruption. However, as S. mutans has been detected in oral cavity of predentate children, the eruption of teeth seems not to be a necessary prerequisite, suggesting that this species may be not confined to dental plaque. Here, we evaluate the ability of S. mutans and S. sobrinus in planktonic and biofilm lifestyle to adhere, invade and survive within human gingival fibroblast (HGF-1) cells. Planktonic and biofilm streptococci adhered and invaded host cells to different extents, showing higher efficiencies of biofilm than planktonic counterparts. Moreover, planktonic and biofilm streptococci showed the same percentage of survival within host cells. Transmission electron and confocal microscopy observations confirmed intracellular localization of planktonic and biofilm bacteria. The adhesion, invasion and survival abilities within human oral cells may be considered S. mutans and S. sobrinus virulence mechanisms to colonize and persist in the oral cavity in the absence of tooth surface.
CELIAC DISEASE, PRIMARY BILIARY CIRRHOSIS AND HELICOBACTER PYLORI INFECTION: ONE LINK FOR THREE DISEASES

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The association between celiac disease (CD) and primary biliary cirrhosis (PBC) has been reported in literature. Recent epidemiological studies showed an increased prevalence of CD in patients with PBC and vice versa. The cause of PBC is unknown. However, considerable evidence points to an autoimmune basis. The role of infectious agents, such as Helicobacter pylori (H. pylori), has been proposed to stimulate antibody cross-reaction with mitochondria of the bile duct cells. We report a case of a 36-year-old woman with diagnosis of CD, PBC and H. pylori infection. Strict adherence to gluten-free diet, associated to ursodeoxycholic acid (UDCA) administration and eradication treatment for H. pylori infection, led to a marked improvement of clinical status. Our experience supports the pathogenetic role of increased intestinal permeability in the course of CD and H. pylori infection to induce PBC. Future studies are needed to clarify this link to, and in particular the role played by abnormal intestinal permeability and infectious agents in the pathogenesis of PBC.

CAN IMMUNE DISORDERS INFLUENCE THERAPEUTICAL APPROACH IN TREATMENT OF EPILEPSY AMONG NEUROLOGISTS? A FIRST CO-OPERATIVE NATIONAL RECOGNITION IN ITALY

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Functional disturbances of the immune system have been detected more often among persons affected by epilepsy than in the general population. In the February-July period of 2007 a specific questionnaire on the relationship between epilepsy and immunological response was sent to 27 specialized Centres for Epilepsy in nine Italian regions. 15,388 epileptic patients attended twenty-seven Centers during this six-month period. 3.3% (n=502) of these patients suffered an immune disease. This is the first national survey on the relationship between epilepsy and immunological response in current clinical practice.
SEVERE GIANT CELL ARTERITIS ASSOCIATED WITH ESSENTIAL THROMBOCYTHEMIA

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Giant-cell arteritis (GCA) is a chronic vasculitis of the elderly usually involving the ophthalmic arteries, which can result in visual loss. High platelet counts may have some pathogenic significance in the obstruction of the ophthalmic circulation and a few cases of associated essential thrombocythaemia and GCA have been described. Here we report a case of severe temporal arteritis associated with essential thrombocythaemia.

IS HYPOGAMMAGLOBULINEMIA A CONSTANT FEATURE IN GOOD’S SYNDROME?

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Thymomas are rare tumors, which can be associated to a variety of paraneoplastic syndromes, including a fatal hypogammaglobulinemia, namely Good’s Syndrome (GS). Although the combination of thymoma and hypogammaglobulinemia is regarded as sufficient for diagnosis of Good’s syndrome, some thymoma patients with a clear clinical picture of immunodeficiency present normal levels of immunoglobulins. We describe the case of a patient, with a 20-year history of thymoma, who underwent several operations and lines of chemotherapy, and suffered from recurrent infections, including one rare skin infection from Pseudoallescheria boydii. The patient constantly presented normal levels of gammaglobulins.

PARANEOPLASTIC SENSITIVE NEUROPATHY ASSOCIATED WITH ANTI-HU ANTIBODIES IN A NEUROENDOCRINE TUMOR OF DUODENUM: A CASE REPORT

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Paraneoplastic sensitive neuropathy is one of the most common presentations among a group of cancer-related disorders known as Paraneoplastic Neurological Syndromes (PNS). PNS likely have an autoimmune etiology since they have been associated with the presence of antibodies against neuronal antigens expressed by tumor cells (such as anti-Hu, anti-Ri and anti-Yo). The tumors most frequently associated with PSN and onconeural antibodies are lung cancer, lymphomas and gynaecological tumors; however, they have also been described in other tumors. We report, for the first time, a case of neuroendocrine tumor of duodenum and PNS associated with anti-Hu antibodies. Moreover, we analyze and discuss the clinical implications that PNS and anti-Hu could have in patients with tumors.
SKIN REACTIONS TRIGGERED BY THE USE OF COSMETIC PRODUCTS IN NON-SPECIFIC LIPID TRANSFER PROTEIN-SENSITIVE PATIENTS

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Nonspecific lipid transfer proteins (nsLTPs) are members of the prolamine superfamily and they are found in pollen and food, as well as in latex. Due to the strong stability both against pepsin digestion and thermal denaturation, sensitisation towards these proteins is often associated with severe systemic reactions (angioedema, urticaria, asthma, anaphylaxis, etc.) following the ingestion of both raw or fresh food and cooked or preserved food. Many studies have shown reactivity towards nsLTPs both via inhalation and orally and in this study we present two cases of nsLTPs-sensitive patients who manifested the immediate onset of skin reactions following the use of cosmetic products containing these proteins. Thus, in order to prevent immediate reactions linked to their use, it is necessary to recommend nsLTPs-sensitive patients to avoid the topical use of products containing these proteins (and obviously the ingestion of foods containing these proteins).

ACUTE PNEUMONIA IN A FIRE-EATER

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Fire-eater’s lung, an acute exogenous lipoid pneumonia, is caused when street performers accidentally inhale pyrofluids. We report the case of a young fire-eater who, 12 hours after inhaling an iso-alkane-based pyrofluid, developed fever, dyspnoea, dry cough and intense right chest pain. Radiographic signs of pneumonia emerged two days later. Computed tomography (CT) scans visualized an irregular area of parenchymal consolidation with an air bronchiologram and peripheral ground-glass opacities in the right middle lobe. The diagnostic work-up included microbiological and lung function tests, optic fibre bronchoscopy and an in-depth cyto-immunological analysis of bronchoalveolar lavage fluid. Symptoms gradually improved over a few days. A CT scan one month later showed the thickened parenchymal area in the right middle lobe had almost completely disappeared.

COMPARISON OF SERUM SPECIFIC IGE AND SKIN PRICK TEST IN POLYSENSITIZED PATIENTS.

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The aim of this study is to evaluate serum specific-IgE in a large group of polysensitized patients with the same SPT result (such as ++++) comparing two diagnostic methods. Six hundred ten patients (310 females; median age 32 years) suffering from allergic rhinitis were studied. Serum specific-IgE were measured by ImmunoCap assay. Skin prick test was also performed. There was a significant difference between serum specific-IgE values in these polysensitized patients. In conclusion, the serum specific-IgE measurement in polysensitized patients seems to be more appropriate than SPT.
Triggering receptor expressed on myeloid cells-1 (TREM-1) and soluble fraction (sTREM-1) are useful markers of infection in adults. Neonates, especially preterm infants, are exposed to high risk of sepsis due to the immature immune system and few data are available regarding TREM-1, mainly focused on the soluble form. We therefore decided to investigate the baseline assessment of TREM-1, membrane and soluble receptors, in preterm newborns without clinical or microbiological evidence of infection, in order to precociously measure the possible changes due to sepsis and compare them to the obtained reference values. Fifty-nine newborns were enrolled in the study. Median and Interquartile range of TREM-1 were: in monocytes 96% [94-98] with 71 Mean Fluorescence Intensity (MFI) [50-94]; in PMNs: 80% [68-87]; soluble TREM-1: 29.1 pg/ml [14.55-103.93]. Monocyte expression and soluble TREM-1 concentrations appeared comparable to healthy adults, while not all PMNs expressed this receptor, possibly due to their immaturity. Birth weight negatively correlated with sTREM-1, while there were no statistical significances with gestational age, maternal age, gender, mode of delivery, patent ductus arteriosus, intrauterine growth restriction, premature rupture of membranes and TREM-1 or sTREM-1. We also reported a statistical relationship between monocyte TREM-1 and surfactant administration and between sTREM-1 and antenatal steroid prophylaxis. Even if untrained, the neonatal immune system of preterm newborns is equipped with TREM-1 system, but further studies are needed to evaluate the functionality in newborns.
LONG-TERM ASSESSMENT OF PLASMA LIPIDS IN TRANSPLANT RECIPIENTS TREATED WITH TACROLIMUS IN RELATION TO FATTY LIVER

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Immunosuppression has improved graft and recipient survival in transplantation but is associated with possible adverse effects including cardiovascular diseases. The impact of tacrolimus on the lipidic profile has been debated for several years. Twenty-nine kidney transplant recipients on tacrolimus treatment were monitored for six years, and multiple laboratory parameters investigating the lipid asset, as well as glucose profile, were carried out. Tacrolimus has been responsible for significant changes in plasma lipid concentrations only for the first six months, but not for the remaining time of observation. Similarly, in the same periods, glycemic imbalance was highlighted. The liver enzyme activity showed a modest derangement during the tacrolimus treatment, suggesting the presence of lipid accumulation in the liver. Fatty liver reversed in the long term follow-up. Tacrolimus, although it is not a completely safe option in the first months of the immunosuppressive protocols in organ transplanted recipients, still retains a certain role in the long-term post-transplantation immunosuppressive approach with high cardiovascular risks.