

Journal Watch

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Fabry disease: a study of 6 hemizygous men and 5 heterozygous women with emphasis on dermatologic manifestations

Larralde M, Boggio P, Amartino H, Chamoles N. Arch Dermatol 2004;140:1440-6.

A series of 11 patients with Fabry disease was studied to determine the relation between its dermatologic and systemic manifestations. Six hemizygous men (age range 19-32 years, average 23.0 years) and five heterozygous women (age range 45-56 years, average 49.9 years) were studied.

For the hemizygous cases, acral pain at an average onset age of six years and angiokeratomas were the earliest manifestations. Elbows, genitalia, extensor surfaces of the arms, waist and back were the most common sites affected by angiokeratomas and were present in 5/6 (83%) hemizygous cases. Cases were diagnosed at an average of 10.8 years after onset of symptoms. The α -galactosidase A activity was much reduced in the hemizygous cases while 4/5 heterozygous women had intermediate levels in peripheral blood leucocytes. Generalised hypohidrosis was present in all of the hemizygotes but was not found in any of the heterozygotes. Angiokeratomas of the trunk and oral mucosa were found in 4/5 (80%) heterozygous women. Asymptomatic echocardiographic findings were found in 4/6 hemizygotes and 3/5 heterozygotes. None of these patients were symptomatic. Other systemic findings included gastrointestinal crisis (5/6 hemizygotes) and corneal opacities (3/6 of

hemizygotes and 3/5 heterozygotes). Renal failure was found in a 32-year-old male. None of the cases had central nervous system involvement.

The authors stressed the importance of angiokeratomas and hypohidrosis as clues to the diagnosis of Fabry disease. Early treatment with human α -gal replacement therapy may reverse some cardiovascular and renal complications.

Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis

Menter A, Gordon K, Carey W, Hamilton T, Glazer S, Caro I, et al. Arch Dermatol 2005;141:31-8.

The efficacy and safety of a 24-week course of efalizumab was evaluated in the treatment of patients with moderate to severe plaque psoriasis. Between weeks 1 and 12, 369 patients were randomised to treatment with subcutaneous efalizumab 1 mg/kg/week, and 187 patients to placebo. In the treatment group, there was a mean PASI improvement of 52.2% at week 12 to 67.2% at week 24. At 12 weeks, 216/369 (58.5%) patients achieved a 50% or greater improvement (PASI 50), and 98 (26.6%) cases reached a 75% or greater improvement (PASI 75) in contrast to placebo (13.9% PASI 50 and 4.3% PASI 75). Between weeks 13 and 24, 516 patients continued to open-label treatment period and all received efalizumab 1 mg/kg/week. At 24 weeks, 245/

368 (66.6%) and 161/368 (43.8%) of efalizumab-treated cases achieved PASI 50 and PASI 75 respectively.

After crossing over from placebo to efalizumab, there was a mean of 53.4% improvement in PASI score. The improvement in other outcome scales at week 12 (Dermatology Life Quality index 49.2%, itching scale 42.2%, Psoriasis symptom assessment severity 47.3% from baseline) was maintained at 24 weeks. The static Physician's Global Assessment of clear or minimal increased from 25.7% to 35.9% during this period. Adverse effects were all mild and included headache, chills, fever, myalgia and generalised pain. The adverse effects were mainly seen in the first two weeks of treatment.

The authors concluded that extending treatment with efalizumab from 12 to 24 weeks increases the efficacy without evidence of cumulative toxicity. This study was sponsored by Genentech Inc (South San Francisco, Calif).

Oral lichen planus and allergy to dental amalgam restorations

Laeijendecker R, Dekker SK, Burger PM, Mulder PG, Van Joost T, Neumann MH.
Arch Dermatol 2004;140:1434-8.

A prospective non-randomised control study was performed to investigate contact allergies in patients with oral lichen planus (OLP) and the effect of amalgam replacement in cases with a positive patch test to ammoniated mercury, metallic mercury or amalgam. Four groups of patients were studied, each consisted of 20 patients. Group A patients had oral lesions in close contact with amalgam fillings while Group B had lesions extended one centimeter from the amalgam fillings. Group C had lesions located at sites unrelated to the amalgam fillings and control group D had signs of contact dermatitis but no

evidence of OLP. Alternative dental restorations consisted of composite resins, glass ionomers, ceramics, and gold.

Amalgam replacement in 13 patients of group A and eight patients of group B led to healing or improvement after a mean interval of three months (range 1 to 4 months). In group C, OLP lesions improved after amalgam replacement in one of two patients. The positive effect of amalgam replacement persisted at a mean follow-up time of four years (range 2-7 years). There was a statistical difference in the incidence of contact allergy to ammoniated mercury and metallic mercury among the four groups ($P < 0.001$) with highest incidence in group A (65%) and lowest incidence in group C (10%), but not amalgam ($P = 0.11$). No contact allergy to organic or inorganic mercury was found in group D or in patients with concomitant cutaneous lichen planus.

The authors therefore recommended patch tests for patients with OLP in close contact amalgam fillings and no associated cutaneous lichen planus. If there is positive patch test reaction to mercury compounds, amalgam fillings should be replaced.

Serum concentration of IL-18 correlates with disease extent in young children with atopic dermatitis

Hon KL, Leung TF, Ma KC, Wong CK, Wan H, Lam CW.
Paediatr Dermatol 2004;21:619-22.

The correlation of interleukin 18 (IL-18) with disease activity in children with atopic dermatitis (AD) was evaluated. Patients under six years of age with a diagnosis of AD according to the criteria of Hanifin and Rajka were studied. The disease severity was assessed by the Scoring Atopic Dermatitis index system (SCORAD). Skin prick tests for whole cow's milk, wheat, soybean,

whole egg, mixed codfish, mixed peanut and *Dermatophagoides pteronyssinus* extract were performed and serum samples for IL-18 were collected.

Nineteen Chinese patients with a median age of 2.2 years (range 0.7-4.6 years, 10 boys and 9 girls) were recruited. Twelve patients had a positive skin prick test and the median SCORAD was 23.9 (interquartile range IQR 18.6-34.8). The overall SCORAD and its extent component correlated with the IL-18 level ($r=0.502$, $p=0.029$) and ($r=0.633$, $p=0.004$) respectively. The median serum IL-18 concentration was 394 pg/ml (IQR 204-612 pg/ml). However, there was no correlation between the intensity ($r=0.371$, $p=0.118$), pruritus ($r=0.311$, $p=0.194$) or sleep components ($r=0.443$, $p=0.057$). There was a significant difference in serum IL-18 levels between mild and severe AD cases (median 221 pg/ml versus 582 pg/ml, $p=0.014$). There was no correlation with atopy, serum total IgE levels or skin prick test response.

Serum IL-18 correlates with the overall and extent component of SCORAD score and may be used to differentiate between mild and severe disease in young children. The authors suggested larger longitudinal studies on the role of IL-18 levels in the management of childhood AD. The study was funded by a Direct Grant for Research from the Chinese University of Hong Kong.

How soon does cutaneous tuberculosis respond to treatment? Implications for a therapeutic test of diagnosis

Ramam M, Mittal R, Ramesh V.
Int J Dermatol 2005;44:121-4.

Clinical records of 60 patients (30 males and 30 females, aged 5-65 years) with cutaneous tuberculosis were reviewed to determine the

appropriate duration of therapeutic trial of antitubercular drugs.

There were 37 patients with lupus vulgaris, followed by scrofuloderma, tuberculosis verrucosa cutis and tubercular ulcer. The diagnostic criteria adopted were typical clinical appearance, a positive tuberculin test and a skin biopsy showing granulomatous dermatitis. Culture for the acid-fast bacilli was not conducted due to poor sensitivity. All patients were given two months of isoniazid 300 mg daily, rifampicin 450 mg daily, ethambutol 800 mg daily and pyrazinamide 1500 mg daily, followed by four months of isoniazid and rifampicin in the same doses. Lesions were regarded as improved if there were a reduction in induration, scaling, verrucosity, erythema, discharge or size. Eight patients were lost to follow up, 48 improved with treatment and four failed to respond. There was perceptible improvement within one month in 21 patients. Due to long follow-up time for various reasons, the remaining 27 patients were found to improve more than 30 days after initiation of treatment. Although it is difficult to ascertain the onset of improvement in the latter group, it was likely that they did so in 30 days, as the time to complete improvement was similar in both groups.

It was concluded that four to six weeks' therapeutic trial with four drugs appears adequate to prove the diagnosis of cutaneous tuberculosis.

Insect sting reactions to bees, wasps, and ants

Steen CJ, Janniger CK, Schutzer SE, Schwartz RA.
Int J Dermatol 2005;44:91-4.

The Hymenoptera order consists of various bees, wasps and ants. Majority of them have poison glands and stinging apparatus. About 0.8-5.0% of individuals may develop a generalised systemic reaction after a Hymenoptera sting. Fire ants are

one of the ant species that can sting and attack human. One study showed that fire ants might pose the greatest risk of anaphylaxis upon stinging. Sting from a fire ant may result in a wheal followed by a sterile pustule after 12-24 hours and the pustule may undergo epidermal sloughing after one to three days. Pustules are often arranged in the shape of a ring, as fire ants pivot on a central axis as they sting repeatedly in the skin.

It is crucial to remove the stinger following a Hymenoptera sting, as the venom sac can continue to exude venom if left adhered to the skin. The best method to remove the stinger is by sweeping the dull blade of a butter knife or the edge of a credit card at an angle almost parallel to the skin surface. Removal by a twister should be avoided as this may compress the venom sac, resulting in injection of additional venom into the skin. Cold compress, oral antihistamine, and mild analgesics may be sufficient for mild reactions, while subcutaneous epinephrine and systemic corticosteroid may be needed for severe reactions and anaphylaxis. Venom immunotherapy is a relatively safe and effective treatment for Hymenoptera venom hypersensitivity and is indicated for people who have had severe reactions and who have detectable venom-specific IgE present in their skin or blood.

Is human herpesvirus 7 the causative agent of pityriasis rosea? – a critical review

Chuh AA, Chan HH, Zawar V.
Int J Dermatol 2004;43:870-5.

Pityriasis rosea has been suspected to be associated with human herpesvirus 7 (HHV-7). This was a medline search study attempting to critically review the evidence and strength for such an association.

Medline was searched under pityriasis rosea and HHV-7 and guidelines of Fredericks and Relman were applied to analyse the data obtained. Thirteen reports were retrieved and reviewed. Only two reports demonstrated HHV-7 DNA in the lesional skin and the plasma of patients suffering from pityriasis rosea, whereas all other reports failed to confirm such finding. Only one report confirmed fewer copies of pathogen-related nucleic acid in healthy controls. Moreover, the number of HHV-7 related nucleic acids was not demonstrated to diminish with resolution of the disease, nor was the disease activity correlated with the number of sequence copies detected. Other clinical manifestations of HHV-7, like roseola infantum, were not found in patients suffering from pityriasis rosea. Furthermore, only one report showed the presence of HHV-7 and HHV-6 m-RNA in infiltrating mononuclear cells in the lesional skin biopsies.

In summary, none of the criteria of Fredericks and Relman was unanimously fulfilled by all or majority of the investigators. It was concluded that there was insufficient evidence to support the association between HHV-7 and pityriasis rosea. Further investigations on the roles of other viruses, virus-virus interactions, and idiosyncratic immunologic response to viral infection and reactivation should be done.

The role of topical calcineurin inhibitors in atopic dermatitis

Alomar A, Berth-Jones J, Bos JD, Giannetti A, Reitamo S, Ruzicka T, et al. ; European Working Group on Atopic Dermatitis
Br J Dermatol 2004;151 (Suppl 70):3-27.

This was a review article to determine the role of topical calcineurin inhibitors in atopic

dermatitis. The safety and efficacy of tacrolimus and pimecrolimus have been extensively assessed in more than 18,000 patients with atopic dermatitis. Short-term vehicle-controlled studies have shown that both drugs were more effective than their vehicles. Long-term studies on atopic dermatitis showed that 89.7% and 92.6% of adults and paediatric patients receiving tacrolimus 0.1% as monotherapy were free from flares over 12 months. Three long-term studies ranged from six months to 12 months reviewed that pimecrolimus significantly reduced the incidence of flare compared with vehicles. Tacrolimus was found to be effective in patients with mild, moderate and severe atopic dermatitis, while pimecrolimus was more effective in mild to moderate diseases. Both short-term and long-term studies also showed that pimecrolimus was less effective than moderately potent corticosteroid in the treatment of atopic dermatitis. Tacrolimus 0.1% has been demonstrated to be more effective than pimecrolimus 1%.

The most common adverse effects for both tacrolimus and pimecrolimus were local reactions, such as skin burning and pruritus. They were more common with tacrolimus and were usually mild to moderate and transient. The evidence available showed that there was a marginal risk of increased infections, but not skin cancer. The incidence of non-melanoma skin cancer in tacrolimus-treated patients was comparable to the healthy general population in the US.

In summary, calcineurin inhibitors offer a solution treatment for atopic dermatitis, in particular, paediatric patients, steroid-phobic patients, sensitive skin regions and regions of constant disease activity.

Pulsed versus continuous terbinafine dosing in the treatment of dermatophyte onychomycosis

Pavlotsky F, Armoni G, Shemer A, Trau H.

J Dermatol Treat 2004;15:315-20.

This retrospective, non-randomised study aimed at exploring the efficacy and safety of using pulsed regimen of oral terbinafine in the treatment of dermatophyte onychomycosis. A total of 260 patients were assigned on a chronological basis to receive continuous (n=105, 250 mg/day for 16 weeks) or pulsed (n=155, 4 pulses, each pulse consisted of 500 mg/day for one week, every four weeks) regimen of oral terbinafine. Mycological and clinical cure were assessed two and three months respectively after completion of the treatment.

For the toenails, the mycological, clinical and complete cure rates were 72.1%, 53.5% and 47.1% in the pulsed regimen versus 82%, 35% and 34% in the continuous regimen ($p=0.091$, 0.0002 , 0.047 , respectively). For the finger nails, the mycological, clinical and complete cure rates were not significantly different between the two regimens: 91.7%, 83.3% and 79.2% in the pulsed regimen versus 100% in all parameters in the continuous regimen. Both regimens were well tolerated. The side effects of the pulsed regimen were similar to those reported in the literature.

In conclusion, the efficacy and safety of pulsed regimen is comparable to continuous regimen for the treatment of onychomycosis. The pulsed regimen has the advantages of lower cost and more convenient to patients. In the future, a randomised and double-blind study is required to confirm the usefulness of pulsed terbinafine regimen and prolonged follow up is required to study the relapse rate.

The diagnostic accuracy of the atopy patch test in diagnosing hypersensitivity to cow's milk and hen's egg in unselected children with and without atopic dermatitis

Osterballe M, Andersen KE, Bindeslev-Jensen C.
J Am Acad Dermatol 2004;51:556-62.

This cohort study aimed at investigating the use of atopy patch test in predicting children's hypersensitivity to cow's milk or hen's egg and compared to the skin prick test, histamine release and specific IgE tests.

A total of 495 unselected three-year-old children were examined and their parents were asked to complete a questionnaire to report food hypersensitivity symptoms. Diagnostic procedures were performed including atopy patch test, skin prick test, blood tests for histamine release and specific IgE, followed by oral challenge in appropriate patients.

In total, 455 (91.9%) children completed both the questionnaire and clinical examination. Respectively 396, 406 and 306 children underwent atopy patch test, skin prick test and blood test for histamine release and/or specific IgE. In children with atopic dermatitis (n=74, 16.3%), 6.8% (5) had food hypersensitivity symptoms as compared to 1.6% (6) of those without atopic dermatitis. Respectively 2.9% and 1.6% of children were possibly hypersensitivity to hen's egg and cow's milk. Oral food challenge was performed in 22 children and hypersensitivity was confirmed in 1.6% to hen's egg and 0.6% to cow's milk. However, no hypersensitivity to either food was predicted by atopy patch test alone. The sensitivity of atopy patch test was only 40%, which was inferior to all other tests (71-88%) while the positive predictive value was 39% which was second to skin prick test (59%).

The authors concluded that atopy patch test could not predict food hypersensitivity to cow's milk and hen's egg that have not been identified by skin prick test, histamine release or serum IgE test.

DNA-based diagnosis of xeroderma pigmentosum group C by whole-genome scan using single-nucleotide polymorphism microarray

Lam CW, Cheung KK, Luk NM, Chan SW, Lo KK, Tong SF.

J Invest Dermatol 2005;124:87-91.

The objective of this study was to investigate the molecular basis of xeroderma pigmentosum (XP) in two unrelated Chinese families. The first female Chinese patient was born to consanguineous normal parents and died of clear cell carcinoma of the ovary at the age of 37. The second female patient was born to non-consanguineous parents and died of disseminated skin cancers at the age of 21.

The genomic DNA of the patients, parents and siblings was extracted from peripheral blood samples. For the first patient, the responsible gene locus XPC was mapped using single-nucleotide polymorphism microarray. She was shown to be homozygous for a nonsense mutation (E149X) by mutational analysis of the XPC gene. The second patient was then screened for XPC mutations. Mutational analysis found that she was a compound heterozygote of 1209delG and Q554X in this gene.

This study identified the first XPC-causing mutations in Chinese patients. In addition, whole-genome scans have particularly advantage in finding disease loci in consanguineous families. The study was partially supported by a grant from the Research Grants Council of the Hong Kong Special Administrative Region, China.