Relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis. A systematic review and meta-analysis

The prevalence of HLA-B*1502 of the Southeast Asian population has been reported to be 8%. The HLA-B*1502 allele is associated with carbamazepine-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The US Food and Drug Administration published an alert to healthcare professionals that the use of carbamazepine in patients with HLA-B*1502 allele can result in severe allergic skin reactions and thus screening for this allele before initiation of carbamazepine therapy in patients of the Asian ancestry is recommended. Nevertheless, the prevalence of HLA-B*1502 varies among different ethnicities in Asian countries. This is a systemic review to determine the relationship between the HLA-B*1502 allele and carbamazepine-induced SJS and TEN in different Asian populations.

The overall odds ratio of the relationship between HLA-B*1502 and carbamazepine-induced SJS and TEN was 79.84 (95% confidence interval, 28.45-224.06). It was found that for Han-Chinese, Thais, Koreans, and Malaysians; the risks of SJS and TEN among carbamazepine users carrying the HLA-B*1502 allele were increased approximately 115-fold, 60-fold, 25-fold and 220-fold respectively. Among individuals of the Western or Japanese ethnicity, no patients with SJS or TEN were carriers of the HLA-B*1502 allele. The authors suggested that the observed racial differences could be explained by the fact that HLA-B*1502 may not be the only gene associated with SJS and TEN in patients using carbamazepine. Another HLA allele (HLA-A*3101), for example, is also related to SJS and TEN. In conclusion, HLA-B*1502 screening in patients requiring carbamazepine therapy is warranted especially in the Han-Chinese, Thai and Malaysian populations.

High-dose isotretinoin treatment and the rate of relapse, relapse, and adverse effects in patients with acne vulgaris

Isotretinoin is the most effective treatment for severe nodulocystic acne vulgaris. Most studies supported a cumulative dose of 120 to 150 mg/kg to decrease the risk of relapse. This was a prospective observational intervention study evaluating the relapse rate of acne vulgaris and the adverse effects of the treatment when using a high cumulative dose of isotretinoin (≥220 mg/kg) compared with a lower dose therapy.

Patients with severe nodulocystic acne resistant to other treatments were prescribed isotretinoin for
a mean of 6.3 months. They were divided into two isotretinoin treatment groups: those who received a cumulative dose of 220 mg/kg or more and those who received less than 220 mg/kg. Patients were then monitored for 12 months after isotretinoin was stopped. At 12 months’ follow-up, the relapse rate of the lower dose treatment group was 47.4% (95% confidence interval, 32.3%-63.0%) compared with 26.9% (95% confidence interval, 18.3%-37.8%) in the high dose group (p=0.03). Almost 100% of the patients in both treatment groups developed cheilitis and xerosis during treatment. Retinoid dermatitis was significantly more common in the high dose treatment group. None of the other adverse effects was significantly different between the two groups.

Limitations of this study were the lack of randomisation or blinding and the patients were not stratified by their acne severity. The authors suggested that higher cumulative doses of isotretinoin were effective for treating acne and decreasing relapse rates without significantly increasing the adverse effects.

Comparison of oral ivermectin vs. lindane lotion 1% for the treatment of scabies

Scabies infestation is the commonest ecto-parasitic infection in human skin. Its highly contagious property makes it an important public health issue with a high prevalence of scabies infestation in resource-poor countries. The symptom of intractable pruritus causes significant disturbance to the host patients. Commonly used treatments in clinical practice include topical (γ-benzene hexachloride [Lindane], permethrin, crotamiton etc.) and systemic agents (ivermectin). Compared to the topical modalities, ivermectin has the advantage of easier administration and a lower cost. The present study compared the efficacy and safety of oral ivermectin with 1% lindane lotion in treating scabies infestation. A total of 148 patients were included in the study and randomised into two treatment groups: (i) single-dosed ivermectin 200 µg/kg p.o. and (ii) two applications (one week apart) of 1% lindane lotion. Subjects who were pregnant, on lactation or under the age of two were excluded. Patients were evaluated at the end of the second and fourth week. The study observed a cure rate of 60.8% at the second week and 89.1% at the fourth week in the ivermectin group. For the topical group, the cure rate was 47.2% and 72.9% at the second and fourth week respectively. The authors concluded that single-dosed ivermectin was as at least effective as two applications of 1% lindane lotion. There was no significant systemic adverse event associated with the use of ivermectin. The study results were in favour of a broader usage of ivermectin based on the cost-effectiveness and an overall better compliance.

Evaluation of total oxidant and antioxidant status in localized and generalized vitiligo

Vitiligo is an acquired disorder of skin pigmentation, affecting 0.1-8.8% of the population worldwide. Patients present with well-demarcated, depigmented patches in localised (focal and segmental) or generalised manner. The condition is associated with the abnormal functioning of melanocytes over the lesional skin. A number of factors including both intrinsic (genetic mutations, autoimmunity, melanocytic destruction, stress etc.) and extrinsic (toxic compounds, phenolic agents, infections, Koebner’s phenomenon) ones have been postulated to trigger or worsen vitiligo. Recent studies have also highlighted the possible
important role of oxidative stress in the aetiopathogenesis of this pigmentary disorder. The present study aimed to determine whether the level of oxidative stress would be different between the generalised and localised form of vitiligo. A total of 31 patients with active vitiligo (14 generalised versus 17 localised) and 38 healthy controls were enrolled into the study. Serum total oxidant status (TOS), total antioxidant status (TAS) and oxidative stress index (OSI) were determined in the cases. Serum TOS is a quantitative estimate of the oxidants present in the serological specimen which oxidises the ferrous ion-o-dianisidine complex to ferric ion. Serum TAS was estimated by the power of the antioxidants presented in bleaching a radical cation [2,2-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid)]. Oxidative stress index represented the systemic oxidative stress and was the calculated ratio of TOS to TAS. The study observed significantly lower TAS and higher TOS and OSI values in patients with vitiligo than those in the healthy controls. However, no statistically significant difference could be detected among these values in patients with generalised and localised disease. The authors concluded that systemic oxidative stress played a role in patients with vitiligo. However, the level of oxidative stress did not correlate with the disease phenotypes. Anti-oxidant therapy may have a role in the management of vitiligo in the future.

Sampling technique is important for optimal isolation of pharyngeal gonorrhoea
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Pharyngeal gonorrhoea (GC) is an important reservoir for Neisseria gonorrhoeae infection because it is usually asymptomatic and plays a role for development of antibiotic resistance through the exchange of genetic material with other commensal Neisseria species. Culture is not sensitive for detection of pharyngeal GC but it provides antimicrobial surveillance when compared to nucleic acid amplification test (NAAT). The study centre in this article provided recommendations on the sampling technique for pharyngeal GC in May 2009. They recommended that 1) swabbing a larger surface, 2) applying more swab pressure, 3) swabbing different anatomical sites and 4) inducing a gag reflex during swabbing, could increase the yield to isolate the pharyngeal GC. The aim of this study was to ascertain whether the recommendations provided could improve pharyngeal GC isolation rates. The study was lasted for six years (the first and second three-year period being before and after the introduction of the recommendations respectively). The result showed that there was a significant increase in detection rates from 1.5% to 2.1% (p=0.004). Specifically, swabbing a larger surface area could increase the detection rate from 1.5% to 2.0% (p=0.02). Applying more swab pressure could increase the rate from 1.5% to 2.5% (p<0.001). Also swabbing both tonsils and oropharynx when compared to tonsils only could increase the detection rate from 1.5% to 2.2% (p=0.002). Inducing a gag reflex implied a vigorous swabbing that also increased the detection yield. To conclude, more thorough swabbing improves the isolation of pharyngeal GC.

Prevalence and morbidity of urethral Trichomonas vaginalis in Japanese men with or without urethritis
Seike K, Maeda SI, Kubota Y, Tamaki M, Yasuda M, Deguchi T.

Trichomonas vaginalis (TV) is one of the microorganisms that cause sexually transmitted infections (STI). It commonly causes vaginitis among women. However its significance in men is in doubt although it may cause non-gonococcal
urethritis (NGU). The aim of this study is to determine the prevalence and morbidity of TV in Japanese men with and without urethritis. A total of 313 men were included during the four-year study period. The first void urine was collected to detect Neisseria gonorrhoeae (GC), Chlamydia trachomatis (CT), Mycoplasma genitalium (MG), Mycoplasma hominis (MH), Ureaplasma parvum (UP), Ureaplasma urealyticum (UU) and TV by PCR based assay. A total of 215 men had symptoms and signs of urethritis including discharge and the presence of five or more polymorphonuclear leucocytes per high-power (x1000) field in Gram-stained urethral smear while 98 men were asymptomatic. Only four men were positive for TV. One each had GC urethritis, CT urethritis and non-CT urethritis; and one was asymptomatic. The prevalence of TV infected men with urethritis was 1.4% and 1.0% in asymptomatic men. The authors commented that these findings suggested that TV might be an uncommon pathogen causing male urethritis and the clinical significance of TV as a pathogen in male NGU remains controversial.

Clinical significance of serum high-mobility group box 1 level in alopecia areata


Alopecia areata (AA) is a relapsing autoimmune hair-loss disorder. Although the exact pathogenesis is still not fully understood, T-cells and cytokines are believed to play an important role. High-mobility group box 1 (HMGB1) is present in all mammalian nuclei at high concentrations and activated HMGB1 has been shown to mediate the release of various cytokines (e.g. TNF-α, IL-1β, IL-6) and chemotactic cell movement in several autoimmune diseases. These cytokines were also shown to play an important role in the pathogenesis of AA in previous studies although the exact pathogenesis of AA has not been comprehensively studied. Hence, the authors aimed to evaluate the clinical significance of HMGB1 in AA.

In this case-control study, healthy subjects with no history of AA, other autoimmune or chronic infectious conditions and those who were not on immunosuppressive agents were recruited as controls. Blood and scalp samples were taken from both patients and controls for HMGB1 level. Clinical parameters including disease type, initial hair pull test results, disease onset and treatment response were documented. A total of 45 patients with AA and 10 controls, (age range: 12-72 years), were recruited. Half of them had patchy alopecia while the remaining had either alopecia totalis or universalis. Around 10% had acute disease (<1 month), while the majority had disease onset for more than six months.

It was found that HMGB1 expression in the scalp specimens was markedly increased in patients with AA, especially in extracellular spaces of the dermis, as opposed to the healthy controls, which were only faintly detected in the dermis. Moreover, serum HMGB1 level was also significantly higher in patients with AA than the healthy controls (8.96 ng/mL vs 0.43 ng/mL, p<0.05). However, its level did not correlate with AA type and the initial hair pull test results. It was significantly higher in patients with more acute disease (p=0.0134) and those with poor treatment response (p=0.002).

The authors concluded that HMGB1 played a significant role in the pathogenesis of AA and served a predictor of prognosis and treatment response. However, the study was limited by the small sample size and further larger studies are required to clarify the exact pathogenesis, clinical significance in AA and its possible role as a new therapeutic target.
Psoriasis is a chronic inflammatory dermatosis. This systemic inflammation also affects the arterial wall, resulting in atherosclerotic plaque formation and hence increases the risk of cardiovascular morbidity. Previous studies have shown that tumour necrosis factor-alpha (TNF-\(\alpha\)) inhibitors reduced cardiovascular events and significantly decreases carotid intima-media thickness (IMT) in rheumatoid arthritis patients.

In this prospective pilot study, the authors aimed at investigating the impact of long-term treatment with TNF-\(\alpha\) inhibitors on arterial IMT in severe plaque-type psoriasis patients.

Patients with severe chronic plaque-type psoriasis, without clinically apparent arthritis and who had failed other systemic treatments were enrolled into the study. They were given TNF-\(\alpha\) inhibitors according to the European protocol. All patients underwent a baseline blood test for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and lipid profile and ultrasonographic measurement of IMT of carotid and brachial arteries. After six months’ treatment, reassessment of clinical response using PASI value, IMT measurement with ultrasonography and laboratory parameters was carried out.

A total of 16 patients (aged 24-66) were recruited. Baseline mean PASI value was 25.64. After six months’ treatment, all subjects achieved PASI 75 and 87.5% achieved PASI 90. Biochemically, there were no significant differences in CRP, ESR and lipid level after treatment. Eleven of the 13 patients with no apparent atherosclerotic plaque at baseline ultrasonography had an increased carotid IMT as compared to to age adjusted normal value. In this group of patients, a significant decrease in IMT value (\(p=0.0002\)) was detected after treatment, which was also significant on individual analysis of carotid (\(p=0.011\)) and brachial (\(p=0.006\)) arteries. On the contrary, in three patients (aged >60) who were found to have calcified plaques on initial assessment, an increasing tendency of carotid and brachial IMT after treatment was observed and the atherosclerotic plaques did not show significant changes.

The authors concluded that TNF-\(\alpha\) inhibitors may have a beneficial impact in those patients with subclinical atherosclerosis but not in those who already had pre-existing atherosclerotic plaques.

This study was limited by a small sample size, a lack of control of potential confounders like cardiovascular risk factors and a lack of precise measurements of vascular inflammation.

Childhood-onset psoriasis: association with future cardiovascular and metabolic comorbidities


This multicentre cross-sectional study was performed in 29 dermatology centres in France from 15 June to 31 October 2011 to evaluate the relationship between childhood-onset psoriasis (COP) and the frequency of cardiovascular risk factors, cardiovascular and metabolic diseases during adulthood. All patients with psoriasis during the study period in these centres were included. Data on patients, psoriasis and its clinical characteristics, cardiovascular risk factors, major adverse cardiovascular events (MACE) and metabolic diseases were recorded for analysis. Finally 2201 patients were included. Fifteen percent of the patients had metabolic syndrome.
and 7% suffered from MACE. Patients with COP had significantly lower rates of BMI, increased waist circumference, obesity, diabetes, dyslipidaemia, hypertension, family history of cardiovascular diseases, MACE and metabolic syndrome. Multivariate analyses retained age as being significantly associated with frequency of cardiovascular and metabolic comorbidities, as well as sex with smoking. However, there was no significant association with age at the onset of psoriasis. Higher frequencies of obesity and psoriatic arthritis were associated with severe psoriasis. The authors concluded that COP was not associated with cardiovascular and metabolic comorbidities in adulthood.

Comparison between autologous noncultured extracted hair follicle outer root sheath cell suspension and autologous noncultured epidermal cell suspension in the treatment of stable vitiligo: a randomised study
Singh C, Parsad D, Kanwar AJ, Dogra S, Kumar R.

This randomised study was conducted at Chandigarh Dermatology Department in India between August 2011 and August 2012 to compare the outcome of non-cultured epidermal cell suspension (NCES) and non-cultured extracted hair follicle outer root sheath cell suspension (NCORSHFS) transplantation in patients with stable vitiligo in terms of repigmentation, patients’ psychosocial quality of life and any adverse events. Thirty patients with refractory vitiligo from this clinic were recruited and were randomly divided into two groups. Fifteen patients with 24 stable vitiligo lesions was treated using autologous NCES and 15 patients with 23 stable vitiligo lesions was treated with NCORSHFS. Excellent repigmentation (90-100%) was observed in 20/24 lesions (83%) and 15/23 lesions (65%) in NCES group and the NCORSHFS group respectively (P=0.154) at week 16 after the transplantation procedure. Similarly, good repigmentation (repigmentation >75%) was observed in 92% of lesions in the NCES group and 78% of lesions in the NCORSHFS group (P=0.425). A highly significant (P<0.001) improvement in DLQI score were observed in both groups though this was not significantly different between the two groups (P=0.244). None of the patients developed serious adverse effects. The authors thus concluded that NCES and NCORSHFS were safe and effective techniques with comparable efficacy.

The clinical significance of BRAF and NRAS mutations in a clinic-based metastatic melanoma cohort

This cohort study was performed in a Swedish university hospital between August 1993 and January 2012 to determine the clinical significance of BRAF and NRAS mutations in patients with metastatic melanoma. Two hundred and thirty-seven tumour samples from 203 patients were screened for mutations in exon 15 of BRAF and codon 61 of exon 2 of NRAS. Seventy-nine patients (41%) harboured BRAF mutations (88% V600E, 10% V600K) and 55 patients (29%) harboured NRAS mutations (48% Q61K, 40% Q61R) among 191 patients with metastatic melanoma lesions. There was a weak trend for a better prognosis in patients with wild-type and NRAS-mutant tumours compared with BRAF V600E-mutant tumours (HR 0.64, 95% CI 0.39-1.04, P=0.07; and HR 0.76, 95% CI 0.48-1.21, P=0.25, respectively). Among those with distant metastatic melanoma, patients with BRAF-mutant tumours displayed a significantly poorer survival compared with 22 patients treated with a BRAF inhibitor (HR 2.35,
The authors thus suggested that BRAF mutation was a weak prognostic factor but a strong predictive factor in metastatic melanoma.

**Pregnancy outcomes after maternal exposure to topical corticosteroids. A UK population-based cohort study**


The safety of topical corticosteroids in pregnancy is not fully understood. It is regarded as pregnancy risk category C by the United States Food and Drug Administration, meaning that adverse fetal effects have been shown in animal studies but no adequate studies in pregnant women are available. Previous studies found that the use of topical corticosteroids in pregnancy might be associated with oro-facial cleft and low birth weight. The aim of the current retrospective cohort study was to investigate whether maternal exposure to topical corticosteroids has adverse effects on pregnancy by examining a comprehensive set of outcomes.

A total of 2,658 pregnant women exposed to topical corticosteroids and 7,246 unexposed pregnant women were enrolled in this study. Any adverse outcomes of oro-facial cleft, low birth weight (birth weight less than 2,500 g), preterm delivery (delivery prior to 37 weeks of gestation), fetal death, low Apgar score (less than 7 at five minutes) and the mode of delivery (normal vaginal delivery, assisted delivery, caesarean delivery) were examined.

No associations of maternal topical corticosteroid exposure with low birth weight, oro-facial cleft, preterm delivery, low Apgar score, fetal death and mode of delivery were discovered in the primary analysis. However, an exploratory analysis showed a significantly increased risk of low birth weight when the dispensed amount of potent or very potent topical corticosteroids exceeded 300 g during the entire pregnancy. The authors suggested that mild or moderate topical corticosteroid were safe treatments in pregnant women if indicated. When potent or very potent topical corticosteroids were required, the amount used should be kept to a minimum and fetal growth should be monitored.