Current Best Evidence

Current best evidence from dermatology literature

Nunley KS, Gao F, Albers AC, Bayliss SJ, Gutman DH. Predictive value of café-au-lait macules at initial consultation in the diagnosis of neurofibromatosis type 1. Arch Dermatol 2009; 145:883-87.

The diagnosis of neurofibromatosis type 1 (NF-1) depends on the presence of 2 or more of the six following features: 6 or more café-au-lait macules (CALM), axillary or inguinal freckling, 2 or more neurofibromas of any type other than plexiform neurofibroma or 1 plexiform neurofibroma, 2 or more Lisch nodules, optic glioma, a characteristic bone lesion and a first degree relative with NF-1. The diagnosis is easy in fully developed cases. The dilemma arises when a child presents with only multiple CALM, which is the initial feature in NF1 and can be seen in many other syndromes.

This retrospective study was undertaken to evaluate the predictive value of number and morphology of CALM in establishing a diagnosis of NF-1 in a future date among a cohort of patients referred to a NF-1 subspeciality clinic and presenting only with CALM. After enrolment, patients were followed up yearly including slit lamp examination of the eyes starting at the age of one year.

One hundred and ten patients were evaluated between the years 2004 and 2007. The median number of CALM at initial presentation was 6. The median age at study entry and median age at last follow- up were 33 months and 76.5 months respectively.

Of the 34 children meeting the diagnostic criteria of NF-1 during study period, 32 did so before the age of 72 months. Mean number of CALM at presentation was 11.8 in those who eventually were diagnosed with NF-1, while it was 4.6 in those who did not meet the criteria for NF-1 during the study period; a statistically significant difference. The percentage of children diagnosed to have NF-1 increased with increasing number of CALMs at initial presentation. The number of children with six or more CALM at presentation was 44 and of them 34 were diagnosed to have NF-1. 'Atypical CALM' (CALM with irregular smudgy border or nonhomogeneous pigmentation) was observed in 42 patients and only 2 of them met the criteria for diagnosis of NF-1.

Comment: Café-au-lait macules (CALM) constitute one of the six diagnostic features for neurofibromatosis type 1 (NF1). According to National Institutes of Health Consensus Development Conference, both the number and size of CALM is important. Number more than six and size more than 5mm in preadolescent children and 15mm in adults is considered to be significant. Quite often we come across children presenting with only CALM without any other feature of NF1. There is scant literature about the final outcome of such patients and available data suggest that all these patients should be followed up yearly with complete physical and neurological examination at each visit. Children with six or more CALM have a greater chance of manifesting other features of NF1 and they do so mostly by six years of age.

In this study an effort was made to analyze the association of number and morphology of CALM with development of NF1. The authors have concluded that children with more than six CALM at presentation have higher chances of fulfilling the diagnostic criteria at a later stage. None of their patients with less than six CALM were diagnosed with NF1 during follow up while more than 2/3rd with six or more CALM ended up with a diagnosis of NF1. Authors have emphasized that higher the number of CALM more are chances of being diagnosed with NF1. Another important observation they have made is about the morphological association of CALM. CALM with uniform color and regular border is strong predictor of NF1 while CALM with irregular color and border is not. The authors did not assess the association between the size of CALM and final patient outcome. These findings pertaining to the number and morphology of CALM should help clinicians in providing proper counseling to Parents

How to cite this article: Jindal R, De D. Current best evidence from dermatology literature. Indian J Dermatol Venereol Leprol 2010;76:87-91.

Received: November, 2009. **Accepted:** December, 2009. **Source of Support:** Nil. **Conflict of Interest:** None declared.

of children having CALMs in the absence of other features of neurofibromatosis type 1.

Kleinpenning MM, Smits T, Boezeman Z, van de Kerkhof PC, Evers AW, Gerritsen MJ. Narrowband ultraviolet B therapy in psoriasis: randomized double-blind comparison of high-dose and low-dose irradiation regimens. Br J Dermatol 2009;161:1351-56.

The optimum dose regimen for narrowband UVB (NBUVB) is yet to be determined. While the inappropriately low dose regimen can require more treatment sessions with suboptimal therapeutic outcome, high dose regimen can lead to side effects with associated increased treatment adjustments and unacceptable side effects decreasing compliance to treatment. The studies that had been undertaken so far on this issue had drawbacks related to study design: retrospective, limited patient number studied and left-right comparison studies.

This prospective study was performed to evaluate the time to clearance in psoriasis patients in a randomized controlled pattern. The patients were divided into two groups who either received low dose or high dose NBUVB. The baseline doses as well as the dose increments were half in low dose regimen (70% of minimal erythema dose vs. 35% of minimal erythema dose and 40% vs. 20% respectively). Irradiation was administered thrice a week and treatment was stopped as soon as clearance (>90% reduction in PASI) of psoriasis was achieved. Patients were reassessed at three months after cessation of treatment for relapse (affected area 50% or more than baseline area).

Patient with mild to moderate psoriasis (initial PASI 9.2±5.3) numbering 109 were randomized. The percentage of patients achieving clearance was 75% and 67% respectively in the high and low dose treatment groups. The mean cumulative doses for clearance of psoriasis in the corresponding groups were 42.5 and 36.7 J/cm^2 respectively. Number of irradiations required were 20.6±6.9 and 24.1±6.1 ($p<0.05$) respectively. There was significantly more numbers of protocol adjustments in high dose group, more commonly due to erythema. Prolonged improvement after treatment cessation was observed in both the groups, but it was more significant in the high dose group.

Comment: Though narrowband UVB (NBUVB) is being used in management of psoriasis for more than two decades now. There is no fixed and standardized regimen for NBUVB to be used in psoriasis. Of late, a number of studies have been conducted to compare high-dose NBUVB with low-dose NBUVB and most of these report equal efficacy of the two regimens. These studies are predominantly left-right comparison studies and do not take into consideration the systemic effects of UVB treatment which acts as an important compounding factor altering the final study outcome. UVB radiations by their effect on Langerhans cells, T-helper cells and *cis*-urocanic acid alter the systemic immunity and this may be responsible for equal response of low-dose and high-dose regimens in left-right comparison study designs.

This study is a prospective, randomized controlled trial in which patients were treated with either a high dose or a low dose NBUVB regimen. A predesigned protocol was used for dose adjustments in case of development of erythema or delay in phototherapy treatment due to other reasons. Statistical analysis showed that there was no difference in the proportion of patients achieving clearance and the cumulative dose to achieve clearance between two groups was comparable. However patients in high dose group needed significantly fewer irradiations (approximately 20%) which mean less cost and less visits to the phototherapy department. With high dose treatment, longer remissions with less relapses were noted which remains the basic aim of all psoriasis treatment protocols. All these findings favor use of high dose regimen over low dose one. One problem which was noted more commonly in high dose group was the need for more protocol adjustments because of erythema which may be painful or may be cosmetically unacceptable. Dose adjustments were required after an average four treatment sessions in high dose group compared to 10 sessions in the low dose group. This high dose NBUVB induced erythema can easily be taken care off by adjusting the standard increment of high dose irradiation protocol after four to five treatment sessions. This will reduce the frequency of burning and patient discomfort. Thus UVB phototherapy in high dose appears to be better than low dose in psoriasis patients.

Dompmartin A, Ballieux F, Thibon P, Lequerrec A, Hermans C, Clapuyt P, Barrellier M, Hammer F, Labbe D, Vikkula M, Boon LM. Elevated D-dimer level in the differential diagnosis of venous malformations. Arch Dermatol 2009;145:1239-44.

Differentiating one vascular malformation from the

other may be difficult. The diagnosis depends on history, clinical examination encompassing color, aspect, localization, palpation, auscultation etc. Imaging studies including Doppler ultrasound, magnetic resonance imaging (MRI), arteriography, X-ray; and skin biopsy histopathology can be valuable aids to the diagnosis. All these investigations are associated with high cost, invasiveness or risk of side effects. This prospective study was undertaken to evaluate the specificity of D-dimer levels for the diagnosis of venous malformation (VM).

Of 195 patients diagnosed purely with VM or a mixed malformation with venous component, 83 (42.6%) had elevated D- dimer levels. Among 85 patients without VM, only 3 (3.5%) had elevated D-dimer. The authors concluded that elevated D- dimer level is highly specific for pure, combined or syndromic VM.

Comment: Vascular malformations are structural defects of development of blood vessels. These can be high flow type including arterial malformations and arteriovenous fistulae, or low flow type including capillary, venous and lymphatic malformations. Other than these mixed malformations particularly capillary-venous, capillary-lymphatic and arterio-venous malformations are also quite common. Our primary aim whenever we encounter a vascular malformation is to identify the nature of the vessels involved. Sometimes in combined malformations, the superficial component is visible clinically but the deep component escapes diagnosis. Most of the times complete evaluation require costly investigations like Doppler ultrasound, MRI and arteriography. D-dimer assay is a biochemical marker for intravascular coagulation. It is an easy and inexpensive biomarker test which if found reasonably sensitive and specific, may form an important component of the investigative profile of patients presenting with vascular malformations.

In this study, the authors have evaluated the levels of D-dimer in 280 patients presenting with cutaneous, subcutaneous and mucosal vascular malformations. Final diagnosis of the type of malformation was made with the help of clinical features; Doppler ultrasound and MRI tests were undertaken whenever indicated. On analyzing the results, it was found that D-dimer assay was highly specific (96.5%) but less sensitive (42.6%) in diagnosing presence of venous malformation. This means that elevated levels of D-dimer positively predicts the presence of underlying venous malformation. A normal level however doesn't rule out an underlying venous malformation. Size of venous malformation and presence of palpable phlebolith positively correlated with elevated D-dimer levels. All patients having negative D-dimer had glomuvenous, lymphatic, capillary malformations (all of which are slow flowing), or fast flowing malformation or Maffucci syndrome. Structure of malformation, depth of its location and propensity for stagnation of blood determines the risk for coagulation. It is also useful in differentiating low flow from high flow venous malformation; that is Klippel Trenaunay syndrome (slow flowing) from Parkes Webers syndrome (fast flowing) without expensive investigations. Mention has also been made of a case where a deeper venous malformation could only be detected in a known patient of capillary malformation based upon persistently elevated D- dimer levels.

Role of D-dimer assay appears to be promising and useful complementary tool for diagnosing vascular anomalies in everyday practice. More studies should be performed to substantiate these findings.

Haslund P, Bangsgaard N, Jarlov JO, Skov L, Skov R, Agner T. *Staphylococcus aureus* and hand eczema severity. Br J Dermatol 2009; 161:772-77.

Hand eczema (HE) often has a chronic or relapsing course. The role of bacterial infections in chronicity and severity of HE remain to be assessed. *Staphylococcus aureus* is an important pathogenic factor for atopic dermatitis (AD) and is associated with the severity of the disease, probably through superantigens from exotoxin-producing *Staphylococcus aureus* strains. Few data are available on the role of *Staphylococcus aureus* in patients with HE.

Aim of this study was to determine the prevalence of *Staphylococcus aureus* in patients with HE compared with controls, and to relate presence of *Staphylococcus aureus*, specific subtypes and toxin production to severity of HE. Bacterial swabs were taken at three different visits from the hand and nose in 50 patients with HE and at the first visit in 50 controls. Exclusion criteria for both cases and controls were AD patients with eczema other than HE, treatment with immunosuppressive medication, use of antibiotics 2 weeks previous to inclusion, employment in the healthcare sector among others. *Staphylococcus*

aureus was subtyped by spa typing and assigned to clonal complexes (CCs), and isolates were tested for exotoxin- producing *Staphylococcus aureus* strains. The Hand Eczema Severity Index (HECSI) was used for severity assessment.

The results showed a significant difference in *Staphylococcus aureus* colonization between patients with HE and controls (48% in patients with HE as compared with 8% in controls). Furthermore, the presence of *Staphylococcus aureus* was related to severity of HE. Patients with *Staphylococcus aureus* on hands had significantly more severe eczema compared with patients without *Staphylococcus aureus* on hands. With respect to the typing of *Staphylococcus aureus*, identical spa types were found in swabs taken at the same time from hands and nose. In 88% of cases, identical spa types were found in the same patient at different visits. Ten different CC types were identified and no specific CC types were related to HE. Toxin-producing strains were not found more frequently in patients with HE than in controls.

Comment: Chronic hand eczema (CHE) has multifactorial etiologies with both endogenous and exogenous factors playing important role. In genetically predisposed individuals environmental exposure to allergens and irritants result in development of CHE. A number of factors result in persistence and severity of HE, one of them is bacterial colonization predominantly by *Staphylococcus aureus*. Recent studies in patients with atopic dermatitis have shown that *Staphylococcus aureus* plays an important role in its pathogenesis. This is mainly through superantigens from exotoxin producing *Staphylococcus aureus* strains. Ever since its role in pathogenesis and chronicity of HE has been speculated but studies in support of same are not many.

In this study, *Staphylococcus aureus* colonization was seen in 48% of patients with HE as compared with 8% of controls. Furthermore, patients with *Staphylococcus aureus* on hands had significantly more severe eczema compared with patients without *Staphylococcus aureus* on hands. With respect to typing of *Staphylococcus aureus*, no association with severity was found, and toxin-producing strains were not found more frequently in patients with HE than in controls. A change in *Staphylococcus aureus* strain had been reported to be associated with increased severity of HE. However, from this study no definite conclusion on this could be drawn as only two patients showed a shift in strain type and in both no evidence of flare in HE was seen.

In AD, exotoxins produced by *Staphylococcus aureus* act as superantigens and result in production of IgE antibodies which leads to inflammation. Whether similar pathogenesis is involved in HE remains to be ascertained. In the present study, toxin producing strains were not more frequent in patients with HE. Therefore, some other mechanisms may be involved. *Staphylococcus aureus* colonization appears to be an important cofactor in chronicity of HE but its role in causation in not certain and further studies including intervention with antibiotics are needed to support it. Another important aspect is that patients with chronic HE harboring *Staphylococcus aureus* and working in the food processing industry or healthcare sector may transmit the microorganism to others.

Wilford C, Fine J, Boyd AS, Sanyal S, Abraham JL, Kantrow SM. Nephrogenic systemic fibrosis: report of an additional case with granulomatous inflammation. Am J Dermatopathol. 2009 Oct 30. [Epub ahead of print]

Nephrogenic systemic fibrosis (NSF) is a recently emerged medical entity almost exclusively seen in patients with renal disease. It occurs in patients who have been exposed to gadolinium containing contrast agents. The spectrum of histologic variants of NSF continues to expand, including a report of NSF mimicking erythema nodosum and several case reports of NSF with giant cells and calcification.

A 36-year-old man with a medical history significant for end stage renal disease presented with skin induration and pain. The patient was exposed to gadolinium when he underwent multiple magnetic resonance imaging studies of the brain and spine in the year 2004-2005 during a prolonged hospitalization for meningitis. Dermatologic symptoms appeared during early 2005, with tightening of the skin of his hands, forearms, and knees. Histopathologic examination revealed dermal fibrosis with hypercellularity. The subcutaneous septa were thickened and showed several foci of granulomatous inflammation composed of multinucleated giant cells and lymphocytes. Although the histopathological pattern was characteristic of erythema nodosum, the history, clinical presentation, and dermal hypercellularity were not consistent for a diagnosis of erythema nodosum.

Comment: Nephrogenic systemic fibrosis was

previously termed as nephrogenic fibrosing dermopathy. With detection of involvement of heart, lungs, tendons, muscle and dura, the term nephrogenic systemic fibrosis was proposed. Since its initial description in the year 2000, many case reports have appeared in the literature. The presentation is with symmetric, distal to proximally extending dermal or subcutaneous fibrosis consequent to increasing dermal and subcutaneous deposition of collagen in a patient with significant renal disease. Almost all the patients give history of prior gadolinium containing contrast exposure. The histopathological findings include dermal fibrosis, thickened collagen bundles and increased fibrocytes extending to involve subcutaneous fat septae. Rare findings include erythema nodosum (EN) like features of septal panniculitis with giant cells and Miescher's radial granulomas.

Authors have reported one such case with EN like granulomatous histopathology and have also reviewed the pathogenic mechanism. Their patient had end stage renal disease and was also exposed to gadolinium containing contrast agent followed by development of skin tightening. Final diagnosis of NSF was reached keeping in mind the medical history, morphology of lesions and histopathology. Scanning electron microscopy and energy dispersive x-ray spectroscopy demonstrated multiple insoluble deposits of gadolinium associated with phosphorous, calcium, and sodium in the dermis and subcutis. The pathogenic mechanism which has been proposed previously is based on transmetalation. In patients with renal disease, clearance of gadolinium after exposure is slow and this leads to displacement of gadolinium from its organic chelate by endogenous calcium, zinc, iron or sodium freeing it to form gadolinium phosphate which incites an inflammatory response in tissues. This further recruits the circulating fibroblasts resulting in fibrosis and collagen deposition. Presence of these fibroblasts has been demonstrated by immunohistochemistry showing accumulation of CD34+ and procollagen 1+ cells in skin biopsy.

NSF is an uncommon disease and should be kept in mind in patients with renal dysfunction. Important differential diagnoses to be excluded include scleroderma, scleromyxedema, lipodermatosclerosis, erythema nodosum and eosinophilic fasciitis. A careful review of each patient's history and clinical features is essential to reach a diagnosis of NSF as no single clinical or histopathological finding is diagnostic of this entity.

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