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C O N T E N T S

## EDITORIAL REPORT - 2007

### JDVL gets into the Science Citation Index Expanded!

Uday Khopkar ..... 1

## EDITORIAL

### Registration and reporting of clinical trials

Uday Khopkar, Sushil Pande ..... 2

## SPECIALTY INTERFACE

### Preventing steroid induced osteoporosis

Jyotsna Oak ..... 5

## REVIEW ARTICLE

### Molecular diagnostics in genodermatoses - simplified

Ravi N. Hiremagalore, Nagendrachary Nizamabad, Vijayaraghavan Kamasamudram ..... 8

## ORIGINAL ARTICLES

### A clinicoepidemiological study of polymorphic light eruption

Lata Sharma, A. Basnet ..... 15

A clinico-epidemiological study of PLE was done for a period of one year to include 220 cases of PLE of skin type between IV and VI. The manifestation of PLE was most common in house wives on sun exposed areas. Most of the patients of PLE presented with mild symptoms and rash around neck, lower forearms and arms which was aggravated on exposure to sunlight. PLE was more prevalent in the months of March and September and the disease was recurrent in 31.36% of cases.

### Comparative study of efficacy and safety of hydroxychloroquine and chloroquine in polymorphic light eruption: A randomized, double-blind, multicentric study

Anil Pareek, Uday Khopkar, S. Sacchidanand, Nitin Chandurkar, Geeta S. Naik ..... 18

In a double-blind randomized, comparative multicentric study evaluating efficacy of antimalarials in polymorphic light eruption, a total of 117 patients of PLE were randomized to receive hydroxychloroquine and chloroquine tablets for a period of 2 months (initial twice daily dose was reduced to once daily after 1 month). A significant reduction in severity scores for burning, itching, and erythema was observed in patients treated with hydroxychloroquine as compared to chloroquine. Hydroxychloroquine was found to be a safe antimalarial in the dosage studied with lesser risk of ocular toxicity.

**Many faces of cutaneous leishmaniasis**

Arfan Ul Bari, Simeen Ber Rahman .....

Symptomatic cutaneous leishmaniasis is diverse in its presentation and outcome in a tropical country like Pakistan where the disease is endemic. The study describes the clinical profile and atypical presentations in 41 cases among 718 patients of cutaneous leishmaniasis. Extremity was the most common site of involvement and lupoid cutaneous leishmaniasis was the most common atypical form observed. Authors suggest that clustering of atypical cases in a geographically restricted region could possibly be due to emergence of a new parasite strain.



23

**Forehead plaque: A cutaneous marker of CNS involvement in tuberous sclerosis**

G. Raghu Rama Rao, P. V. Krishna Rao, K. V. T. Gopal, Y. Hari Kishan Kumar, B. V. Ramachandra .....

In a retrospective study of 15 patients of tuberous sclerosis, eight patients had central nervous system involvement. Among these 8 cases, 7 cases had forehead plaque. This small study suggests that presence of forehead plaque is significantly associated with CNS involvement.

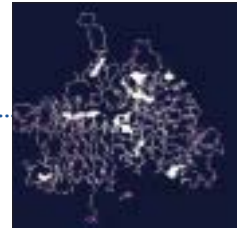


28

**BRIEF REPORTS**

**Ligand-binding prediction for ErbB2, a key molecule in the pathogenesis of leprosy**

Viroj Wiwanitkit.....



32

**SCORTEN: Does it need modification?**

Col. S. S. Vaishampayan, Col. A. L. Das, Col. R. Verma .....

35

**CASE REPORTS**

**Universal acquired melanosis (Carbon baby)**

P. K. Kaviarasan, P. V. S. Prasad, J. M. Joe, N. Nandana, P. Viswanathan .....



38

**Adult onset, hypopigmented solitary mastocytoma: Report of two cases**

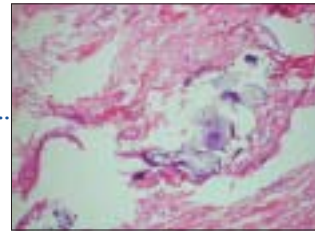
D. Pandhi, A. Singal, S. Aggarwal.....



41

**Incidental finding of skin deposits of corticosteroids without associated granulomatous inflammation: Report of three cases**

Rajiv Joshi .....



44

**Erythromelanosus follicularis faciei et colli: Relationship with keratosis pilaris**

M. Augustine, E. Jayaseelan .....



47

**Naxos disease: A rare occurrence of cardiomyopathy with woolly hair and palmoplantar keratoderma**

R. Rai, B. Ramachandran, V. S. Sundaram, G. Rajendren, C. R. Srinivas .....



50

**Granular parakeratosis presenting with facial keratotic papules**

R. Joshi, A. Taneja .....



53

**Adult cutaneous myofibroma**

V. Patel, V. Kharkar, U. Khopkar .....



56

**LETTERS TO THE EDITOR**

**Extragenital lichen sclerosus of childhood presenting as erythematous patches**

N. G. Stavrianeas, A. C. Katoulis, A. I. Kanelleas, E. Bozi, E. Toumbis-Ioannou .....



59

**Leukocytoclastic vasculitis during pegylated interferon and ribavirin treatment of hepatitis C virus infection**

Esra Adisen, Murat Dizbay, Kenan Hize, Nilsel İlter .....

60

**Poland's syndrome**

Saurabh Agarwal, Ajay Arya..... 62

**Hereditary leiomyomatosis with renal cell carcinoma**

Sachin S. Soni, Swarnalata Gowrishankar, Gopal Kishan Adikey,  
Anuradha S. Raman ..... 63

**Infantile onset of Cockayne syndrome in two siblings**

Prerna Batra, Abhijeet Saha, Ashok Kumar ..... 65

**Multiple xanthogranulomas in an adult**

Surajit Nayak, Basanti Acharjya, Basanti Devi, Manoj Kumar Patra ..... 67



**Bullous pyoderma gangrenosum associated with ulcerative colitis**

Naik Chandra Lal, Singh Gurcharan, Kumar Lekshman, Lokanatha K..... 68



**Sporotrichoid pattern of malignant melanoma**

Ranjan C. Rawal, Kanu Mangla..... 70



**Acitretin for Papillon-Lefèvre syndrome in a five-year-old girl**

Didem Didar Balci, Gamze Serarslan, Ozlem Sangun, Seydo Homan ..... 71

**Bilateral Becker's nevi**

Ramesh Bansal, Rajeev Sen..... 73



**RESIDENTS' PAGE**

**Madarosis: A dermatological marker**

Silonie Sachdeva, Pawan Prasher ..... 74

**FOCUS**

**Botulinum toxin**

Preeti Savardekar ..... 77

**E-IDVL**

**Net Studies**

**A study of oxidative stress in paucibacillary and multibacillary leprosy**

P. Jyothi, Najeeba Riyaz, G. Nandakumar, M. P. Binitha ..... 80

**Clinical study of cutaneous drug eruptions in 200 patients**

M. Patel Raksha, Y. S. Marfatia ..... 80

**Net case**

**Porokeratosis confined to the genital area: A report of three cases**

Sujata Sengupta, Jayanta Kumar Das, Asok Gangopadhyay ..... 80

**Net Letters**

**Camisa disease: A rare variant of Vohwinkel's syndrome**

T. S. Rajashekar, Gurcharan Singh, Chandra Naik, L. Rajendra Okade ..... 81

**Cross reaction between two azoles used for different indications**

Arika Bansal, Rashmi Kumari, M. Ramam ..... 81

**Net Quiz**

**Asymptomatic erythematous plaque on eyelid**

Neeraj Srivastava, Lakhan Singh Solanki, Sanjay Singh ..... 82



**QUIZ**

**A bluish nodule on the arm**

Ragunatha S., Arun C. Inamadar, Vamseedhar Annam, B. R. Yelikar ..... 83



**REFEREE INDEX-2007**

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## Botulinum toxin

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### INTRODUCTION

Cosmetic dermatology is fast emerging as the preferred subspecialty of budding dermatologists. Its recent and sudden rise in popularity has much to do with the efficacy of botulinum toxin that has become a part of lay person's vocabulary.

### HISTORY

The word "*Botulus*" in Latin means "sausage".<sup>[1]</sup> Botulism is a bilaterally symmetric descending neuroparalytic illness which derives its name from the ingestion of spoiled sausage in Napoleonic times.<sup>[1]</sup> Food-borne botulism and its clinical symptoms were first described by the German physician, Justinus Kerner during the period between 1817-1822.

In 1946, Schantz isolated botulinum toxin type A in its crystalline form<sup>[2]</sup> and in 1970, it was first used for strabismus and blepharospasm due to its property to paralyze muscles. In 1989, botulinum toxin got the Food and Drugs Administration's (FDA) approval and is now used worldwide for therapeutic and cosmetic purposes, the quantity of the toxin used varying according to the size of the muscle and the desired action.

Botulinum toxin (Botox®) is a neurotoxin produced by fermentation of the Hall Strain of *Clostridium Botulinum* type A, a Gram-negative, anaerobic bacterium.<sup>[1]</sup> The growth medium contains casein hydrolysate, glucose and yeast extract. Dialysis purifies the toxin complex (neurotoxin and several accessory proteins) from the culture solution. Serologically, there are eight distinct types designated as A,

B, C1, C2, D, E, F and G.

### PHARMACOKINETICS

Patients usually notice a clinical effect 1-5 days following injection and the peak effect is observed by 1-2 weeks. A 10-unit injection into the frontalis muscle produces a circular area of paresis with a radius of approximately 1.5 cm making the spacing of injection sites very important. Clinical effects are expected to last 2-6 months when the amount of Botox® used only serve to soften the movements of the muscles.

When the recommended dosage is used, Botulinum toxin Type A is not expected to be present in the peripheral blood at measurable levels following intramuscular (IM) or intradermal injection. The recommended quantities of neurotoxin administered at each session do not usually result in systemic effects or muscle weakness in patients unless they have neuromuscular dysfunction. However, subclinical systemic effects have been shown by single-fiber electromyography after appropriate IM doses of botulinum toxin to produce clinically observable local muscle weakness.<sup>[3]</sup>

Effects of botulinum toxin can get potentiated with the administration of aminoglycosides or other agents interfering with neuromuscular transmission, *i.e.*, curare-like compounds. Different botulinum toxin serotypes, *e.g.*, Myobloc/Neurobloc® (2500/5000 unit vials) or Dysport® (500 units per vial) are not interchangeable as their simple dose ratios are inappropriate. They should not be administered at the same time or in the same person as

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excessive neuromuscular weakness may result from their administration.<sup>[3]</sup> It is advised not to freeze Botox® once reconstituted as ice crystals may form which damage the toxin and reduce the potency.

## MECHANISM OF ACTION

Neurotransmission at the neuromuscular junction occurs once acetylcholine is released from the presynaptic nerve terminals. The botulinum toxin (BT) blocks acetylcholine release and causes chemical denervation.<sup>[4]</sup> Initially, binding of the toxin to specific receptors on the surface of the presynaptic nerve cell surface occurs in approximately 30 minutes. Then, due to endocytosis, the plasma membrane of the nerve cell invaginates around the toxin-receptor complex, forming a toxin-containing vesicle inside the nerve terminal. The disulfide bond is then cleaved within the toxin-containing vesicle and the 50-kDa light chain of the toxin molecule is released across the endosomal membrane of the endocytic vesicle into the cytoplasm of the nerve terminal. Finally, the 50-kDa light chain (of serotypes A and E) cleaves a cytoplasmic protein (SNAP-25) required for the docking of acetylcholine vesicles on the inner side of the nerve terminal plasma membrane. This blocks acetylcholine release into the neuromuscular junction resulting in paralysis of that muscle. The clinical effects of botulinum toxin injections last for 2-6 months after which, the inactivated terminals slowly recover function in an average period of four months. Then, the new nerve terminal sprouts and their end plates regress. Recovery of inactivated terminals appears to be the basis of the loss of clinical effects several months after the injection.

## INDICATIONS AND USES

For cosmetic purposes, BT is commonly used on the upper half of the face to target horizontal forehead lines, glabellar frown lines and lateral canthal lines (Crow's Feet). It is also used for temporal brow lift, bunny lines (Levator labia superioris) and nasal flare.<sup>[3]</sup>

An adjunctive use of BT is to provide presurgical chemodenervation of the brow depressor muscles giving better results with surgical repositioning of the brow. Other uses of BT<sup>[3,5]</sup> include achalasia, blepharospasm, cervical dystonia, detrusor hyperreflexia, essential tremor, hemifacial spasm, hyperhidrosis, migraine and headache, myofascial pain syndrome, occupational dystonia, pain due to muscle spasm, rectal fissure, sialorrhea, spasmodic dysphonia, strabismus, spasticity and thoracic outlet syndrome.

Advanced uses of BT include mental crease, popply chin, platysmal bands, horizontal neck lines, hypertrophic mandibular angles and facial asymmetry.

## CONTRAINDICATIONS

These include prior allergic reaction, injection into areas of infection or inflammation, pregnancy (Category C drug: safety for use during pregnancy has not been established) or lactation. Women who inadvertently were injected during pregnancy, this far have had uneventful deliveries and to date, no teratogenicity has been attributed to botulinum toxin. Relative contraindications include disorders of the neuromuscular junction, myasthenia gravis, Eaton Lambert syndrome,<sup>[6]</sup> and disorders with muscle weakness like multiple sclerosis, amyotrophic lateral sclerosis.

## DOSAGES AND ADMINISTRATION

Depending upon the size of the muscle and action required, the amount of BT used varies in cosmetic use or other purposes. The small muscles of the face require 3-10 units depending on the bulk of the muscle. Usually < 100 units are used for cosmetic indications and 300-600 units for other indications. The human lethal dose for Botox® type A purified neurotoxin complex is estimated to be approximately 3000 units.<sup>[4]</sup>

The vial is to be stored in a freezer  $\leq -5^{\circ}\text{C}$ . Once reconstituted, it is to be refrigerated at  $2-8^{\circ}\text{C}$ . After reconstitution, Botox® can be used for a month if kept refrigerated. The diluent, a sterile saline solution, is injected gently into the vial to avoid agitation or foaming as the toxin can get easily denatured. One hundred units are commonly diluted in 2-4 ml of diluent. Theoretically, more concentrated solutions reduce reliability in delivering a specific unit dose and more dilute solutions lead to greater diffusion of the toxin. Preferably, a 30-gauge needle is used for injection purposes.

## ADVERSE EFFECTS

- 1) Lid ptosis which usually resolves in 1-6 weeks may occur if BT is injected too medially, within a centimeter from the lateral orbital rim margin.<sup>[6]</sup> When this occurs, apraclonidine 0.5% eyedrops (Albalon®) administered every three hours will temporarily resolve symptoms and phenylephrine 2.5% eye drops can be used if apraclonidine is not available.
- 2) Brow ptosis may occur if the injection is close to or



within a centimeter of the eyebrow. Consideration of infrabrow injection at the arch to raise the brow has been suggested.

- 3) A local temporary swelling like upper eyelid edema sometimes occurs in Asian patients.<sup>[6]</sup>
- 4) Bruising: This can be avoided by advising patients to avoid aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), *gingko biloba* and vitamin E starting ten days prior to BT treatment.
- 5) Headaches
- 6) Diplopia - rare
- 7) Excessive brow elevation or “quizzical” brows,<sup>[5]</sup> which can be corrected with 2-4 units of Botox<sup>®</sup> injected into the frontalis, two centimeters above the lateral brow.

Chemodenervation with botulinum toxin has become an integral part of the facial plastic armamentarium.<sup>[5,6]</sup> Traditional treatment for deformities on face by surgical intervention is slowly being replaced by BT wherever possible. With a complete understanding of facial anatomy

and muscular interactions, and pharmacokinetics of botulinum toxin, the dermatologist or plastic surgeon can produce magnificent results with botulinum toxin.

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