Drug Induced Syndromes: An Overview

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ABSTRACT

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Many drugs have come into the market in recent years and its usage is increased for multiple disorders which in turn leads to poly pharmacy and increased drug related problems. One such drug related problem is Drug-induced syndrome. These syndromes are one of the major problems in the health care sector. Drug related problems are found to be a reason for hospital admission and also for an increased patients stay in the hospital. The syndromes can be associated with any pathological conditions or may be drug related. This overview article provides the information regarding the different drug induced syndromes with its causative agents, clinical manifestation and therapy.

Keywords: Drug induced syndrome, drug related problem,

INTRODUCTION

The word "Syndrome" derived from the Greek word sundrom, which means concurrence of symptoms, or from word sundromos, which means running together. Syndrome is a set of symptoms occurring together. In medical context syndromes are classified as syndromes caused due to environmental causes, cardiovascular, iatrogenic, neoplastic, congenital, endocrine, pulmonary, infectious, renal, neurological, gastrointestinal, reticulo-endothelial, hematologic, others.[1]

Drug-induced syndromes or iatrogenic (physician induced) syndromes are produced by drugs themselves and leads to certain pathological changes. These are temporally related with starting a drug, and the symptoms and signs generally regress with its discontinuation.[2,3] The increasing number and complexity of diagnostic procedures and therapeutic agents, monitoring of untoward events is essential, and attention should be paid to educational efforts to reduce the risks of iatrogenic illness.[4] Important risk factors for adverse drug events or reactions included polypharmacy, drugs with narrow therapeutic range, renal elimination of drugs, age >65 years and use of anticoagulants or diuretics. Since medication errors are strong risk factors for preventable adverse drug events or reactions, strategies have to be put in place for their reduction. Such strategies include ensuring that all persons involved in the medication process (nurses, pharmacists and physicians) have good pharmacological knowledge, computerization of the entire medication process, and the engagement of a sufficient number of clinical pharmacists on the wards.[5]

The drugs with single or combination can leads to iatrogenic syndromes with severity ranging from mild to severe. Awareness should bring towards health care professionals for the management of drug induced syndromes. This article brings brief description of drug induced syndromes including causative agents, symptoms and management.

Drug Rash with Eosinophilia and Systemic symptoms Syndrome (DRESS): DRESS syndrome reflects a serious hypersensitivity reaction to drugs and has been classified under a delayed type IVb hypersensitivity reaction, where T helper type II cells play a significant role.[6] (Fig 1)

Causative drugs: Anticonvulsants, Sulfonamides, Dapsone, Allopurinol, Minocycline, Gold, Hydroxychloroquine (HXQ) Sulfate, Isoniazid, Rifampicin, Ethambutol and Pyrazinamide.[6,7]

Symptoms: Fever is usually present. Skin eruption may vary from a diffuse maculopapular inflammatory rash to erythroderma, Stevens–Johnson syndrome or erythema multiform. Concerning organ involvement, lymph nodes, liver and kidney are frequently affected; lung and heart are involved in a minority of the cases.[6]

Treatment: Causative drugs should be withdrawn as a part of the treatment and steroids are useful for patients with life-threatening visceral manifestations such as interstitial Pneumonitis or nephritis. In milder cases, topical steroids improve the skin manifestations. Interferon-α is also useful for long-lasting DRESS.[6,7]

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Serotonin Syndrome: Serotonin Syndrome is a toxic state largely attributable to the changes in the sensitivity of serotonin receptor system, resulting from increased serotonergic activity in central neurologic system, due to serotonergic agents either in overdose or in combination.[8]

Causative drugs: L-tryptophan, Amphetamine, Lithium, Dextromethorphan, Merperidine, Fluoxetine, Trazodone, Venlafaxine, Buspirone.[9]

Symptoms: Neuromuscular (clonus, myoclonus, tremor, hyperreflexia) and autonomic (fever, mydriasis, tachycardia, tachypnea) symptoms, mental status changes (confusion, agitation) and may result in death in severe cases.[9]

Treatment: The main and foremost therapy is the cessation of the medication and the syndrome usually resolves within 24 hours after the withdrawal of the causative drug. If serotonin syndrome has occurred as a result of an acute overdose, activated charcoal may be beneficial soon after the ingestion. Supportive care is the mainstay of treatment. Hyperthermia should be treated with aggressive external cooling measures such as ice, mist, fans and a cooling blanket. Rigidity, seizures, and agitation are treated with Benzodiazepines. One study revealed that the severe symptoms can be successfully treated with Cyproheptadine (5-hydroxytryptamine antagonist).[9]

Red Man Syndrome (Red-Neck Syndrome /RMS): Red-Neck syndrome is characterized by pruritus; erythema of the face, neck, and upper torso; and in severe cases, angioedema and cardiovascular collapse.[10, 11]

Causative drugs: Vancomycin, Ciprofloxacin, Amphotericin B, Rifampicin and Teicoplanin.[11]

Symptoms: Sensation of burning and itching, agitation, dizziness, headache, chill, fever and perioral paresthesia.[11]

Treatment: The effects of red man syndrome can be relieved by antihistamines. Pretreatment with hydroxyzine can significantly reduce erythema and pruritus. Diphenhydramine hydrochloride intravenously or orally can abort most of the reactions.[11]

Blue-Gray Syndrome: Blue gray syndrome is an amiodarone related hyperpigmentation considered as a skin storage disease secondary to drug deposition.[12]

Causative drug: Amiodarone.[12, 13, 14]

Symptoms: Blue-gray skin pigmentation, dyspnea, cough and fever.[12, 13, 14](Fig 2)

Treatment: Discontinuation of the causative agent without introducing other medication is considered as the most practiced therapy in clinical setup. Careful and regular long term follow-up is mandatory.[13, 14]

Severe Dapsone Hypersensitivity Syndrome: Adverse reactions to Dapsone**,** a potent anti-inflammatory, anti-parasitic compound, first line drug for leprosy include dramatic, generalized hypersensitivity syndrome termed as Dapsone syndrome which has a frequency of 0.2% - 0.5% in patients on Dapsone therapy typically begins with several weeks of starting the drug.[15]

Causative drug: Dapsone.[15, 16, 17]

Symptoms: High fever lasting for about 4-5 days associated with malaise, sore throat, dysphagia, productive cough, and a pruritic rash, methamoglobinemia and hemolytic anemia.[16] (Fig 3) .

Treatment: Patients can be treated with corticosteroids both orally (Prednisolone 40 mg/d) and topically (Beclomethasone dipropionate ointment 0.025%, 2 times a day). Cetirizine and Hydroxyzine are also given for the management of Dapsone syndrome.[16]

Neuroleptic Malignant Syndrome (NMS): NMS is a rare, but sometimes fatal, adverse reaction of neuroleptics characterized principally by fever and rigor.[18]

Causative drugs: Butyrophenones, Phenothiazines, Thioxanthenes, Hydroxyzine, Reserpine;, Amitriptyline, Amoxapine, Desipramine, Maprotiline, Phenelzine, Tranylcypromine, Diazepam, Lorazepam, Carbamazepine, Phenytoin, Amantadine, Bromocriptine, Levodopa, Lithium.[18]

Symptoms: Dopaminergic blockade cardinal features including autonomic dysfunction, altered mental status, muscular rigidity, hyperthermia, cogwheel rigidity, dyskinesia, dysphagia, festinating gait, lead pipe muscle rigidity, oculogyric crisis and opisthotonos are seen in patients.[19]

Treatment: Strong suspension of NMS neuroleptics should be done immediately. Supportive measures are of great importance especially rehydration and cooling. Bromocryptine and Dantrolene given in divided doses orally or parenterally up to 60mg per day.[20]

Nicolau Syndrome (Livedoid Dermatitis/NS): Nicolau Syndrome is a rare adverse drug reaction with unknown pathogenesis at the site of intramuscular drug injection.[21]

Causative drugs: Non-steroidal Anti-Inflammatory Drugs, Corticosteroids, and Penicillin.[21]

Symptoms: Pain around the injection site soon after injection, followed by erythema, livedoid patch, haemorrhagic patch, finally resulting into the necrosis of skin, subcutaneous fat, and muscle tissue.[22](Fig 4)

Treatment: Treatment ranges from local care to surgical intervention. Antibiotic use is restricted to cases with signs

and symptoms of infection. Use of Vasoactive agents (Pentoxyphylline) together with hyperbaric oxygen may be beneficial considering the vascular pathogenesis. Vasospasm may be relieved by the phosphodiesterase inhibiting action of pentoxyphylline. Topical corticosteroids are effective for acute tissue inflammation. Wound care, debridement, dressings, and flap reconstruction are ideal surgical measures. Failure to recognize the extent of fat necrosis and poor blood supply leads to inadequate debridement and poor wound healing. The patients are then prone to repetitive cycles of infection leading to extensive scarring, soft tissue indentation, and unsightly skin grafts.[23]

Warfarin-Induced Skin Necrosis: Warfarin-induced skin necrosis due to oral anti-coagulation therapy causes injury to the skin. Cutaneous injury from warfarin begins as localized paresthesias with an erythematous flush, progresses to petechiae and hemorrhagic bullae, and may eventually result in full-thickness skin necrosis.[24]

Causative drug: Warfarin.[24,25,26]

Symptoms: Patients may initially experience local paresthesias with an erythematous flush followed by intense pain and rapid development and coalescence of petechiae, with concomitant accumulation of subcutaneous edema resulting in a peaud'orange appearance. During the first 24 hours after the first sign of skin lesions, hemorrhagic bullae may occur, which signals irreversible tissue injury. Full-thickness skin necrosis is the end stage of cutaneous injury.[24] (Fig 5)

Treatment: Vitamin K intravenously and fresh frozen plasma (FFP) can be given to the patient to reverse the effects of the warfarin.[24]

Sweet Syndrome: Sweet syndrome is a condition associated with autoimmune phenomena including relapsing polychondritis, drug-induced lupus, and development of Anti-Neutrophil Cytoplasmic Antibodies (ANCAs).[27]

Causative drugs: Abacavir, All-Trans Retinoic Acid, Bortezomib, Carbamazapine, Celecoxib, Clozapine, Diclofenac, Diazepam, Furosemide, Hydralazine, Imatinib, Lenalidomide, Minocycline, Nitrofurantoin, Norfloxacin, Ofloxacin, Pegfilgastrin, Propylthiouracil, Quinupristin, Dalfopristin, Trimethoprim-Sulfamethoxazole.[27]

Symptoms: Rapid onset of fever, leukocytosis, painful erythematous and edematous papules, plaques and nodules infiltrated by neutrophils.[27]

Treatment: Causative drugs should be suspended and systemic corticosteroids can be given to the patient for the management of lesions.[28]

Stevens - Johnson syndrome (SJS): SJS is a well-recognized immune complex mediated hypersensitivity reaction that affects all age groups. It has classic systemic, mucosal and dermatologic manifestations.[29]

Causative drugs: Ibuprofen, Allopurinol, Chloroquine, Penicillamine, Sulfasalazine, Carbamazepine, Etosuximide, Phenobarbital, Phenytoin, Valpoic Acid, Amoxicillin, Imipenem, Ciprofloxacin, Clindamycin, Doxycyclin, Erythromycin, Sulfadiazine, Sulfamethoxazole-Trimethoprim, Dapsone, Fluconazole, Nystatin, Nevirapine, Abacavir, Efavirenz, Tamoxifen, Verapamil, Enalapril, Acetazolamide.[30,31,32]

Symptoms: Erythema with bullous, eroded lesions of skin and mucous membrane and cholestatic liver disease.[29]

Treatment: Withdrawal of the causative drugs, rapidly initiating supportive care in an appropriate setting and the management of fluid and electrolyte requirements. Treatment started with IV fluids and combination of corticosteroid is used.[29]

Toxic Epidermal Necrolysis (Lyell Syndrome/TEN): TEN is a severe adverse cutaneous drug reaction that predominantly involve the skin and mucous membranes. It is an autoimmune blistering disease, including linear IgA dermatosis and paraneoplastic pemphigus but also pemphigus vulgaris and bullous pemphigoid, acute generalized exanthematous pustulosis (AGEP), disseminated fixed bullous drug eruption and staphyloccocal scalded skin syndrome (SSSS).

Causative drugs: Sulfonamides, Pyrazolones, Barbiturates, Ibuprofen, Allopurinol and Carbamazepine.

Symptoms: Hyper and hypopigmentation of the skin, nail dystrophies, ocular complications, trichiasis, symblepharon, distichiasis, visual loss, entropion, ankyloblepharon, lagophthalmos and corneal ulceration.

Treatment: Prompt identification and withdrawal of the causative drug, systemic steroids, high-dose intravenous immunoglobulin Ciclosporin, and Cyclophosphamide (CPP).[31]

Rabbit's Syndrome (RS): RS is a rare movement disorder generally associated with prolonged use of antipsychotics characterized by involuntary, rhythmic, fast and fine movements of the oral and masticatory muscles along the vertical axis of the mouth. It takes its name from an unusual resemblance to the chewing motions of rabbits.[33]

Causative drugs: Methotrimipramine, Benzotropine, Mesoridazine, Clorazepate, Chlorpromazine, Trifluoperazine, Lithium, Clocapramine, Propericiazine, Levopromazine, Bromperidol, Sulpiride, Thioridazine,

Haloperidol, Zuclopentixol, Biperidene, Perphenazine, Amitriptyline, Paroxetine, Risperidone, Clozapine, Olanzapine, Aripiprazole.[33]

Symptoms: RS is characterized by involuntary and rhythmic movements along the vertical axis of the mouth occur at a frequency of approximately 5 Hz. The oral movements are often accompanied by a popping sound that is produced by the rapid smacking on one's lips. This syndrome is limited exclusively to the territory of the oral and masticatory muscles and does not involve the tongue.[34]

Treatment: Rabbit's Syndrome typically responds favorably to anticholinergic agents such as Benztropine, Biperiden, Procyclidine and Trihexyphenidyl. This Syndrome typically disappears few days after the introduction of an anticholinergic agent, but can, on occasion, reappear after stopping anticholinergic medications.[34]

Vanishing Bile Duct Syndrome (VBDS): VBDS is a rare cause of progressive cholestasis and is mostly related with drugs. Drugs act as a hapten and produce autoantibodies against cytokeratin which is in the bile duct, skin, conjunctival epithelium and orogenital mucosa. Autoantibodies destroy biliary apparatus with resultant disappearance of intrahepatic bile duct.

Causative drugs: Anticonvulsants, Sulfonamides, Penicillins, Allopurinol, Nonsteroidal Anti-Inflammatory Drugs.

Symptoms: Cholestasis, pruritis, weight loss, malaise, disappearance of intrahepatic bile duct

Treatment: The therapy involves mainly the withdrawal of the causative agent, supportive care, and the usage of immunosuppressants. Steroids, choleretic agents are also useful for the management purpose.[29]

Hand-Foot Syndrome (Palmar-Plantar Erythrodysaesthesia/HFS): Palmar-Plantar Erythrodysaesthesia is a relatively common adverse effect of chemotherapeutic drugs.

Causative drugs: 5-Fluorouracil, Doxorubicin, Docetaxel, Idarubicin, and Cytarabine.

Symptoms: Erythema, tenderness, tingling, numbness, dry rash and desquamation over the palms and soles. (Fig 6)

Treatment: The management of hand-foot syndrome entails immediate discontinuation of the causative drug and symptomatic care. Steroids and pyridoxine show good response in patients. The causative drug may be cautiously re-introduced in a lower dose.[35]

Purple Glove Syndrome (PGS): Purple Glove Syndrome is caused by intravenous administration of phenytoin resulting in soft tissue injury at the site of injection leading to oedema and purplish-black discoloration of the hand.

Causative drugs: Phenytoin.

Symptoms: Intense pain, purplish black discoloration and oedema at the site of injection.

Treatment: The management of PGS is mainly conservative, which includes limb elevation and physiotherapy. Use of low concentration local anaesthetic for brachial plexus block has an added advantage of preserving motor function to facilitate physiotherapy in addition to providing adequate analgesia and relief of vasospasm. [36]

Creutzfeldt-Jakob like Syndrome (CJS): CJS syndrome commonly with lithium products is characterisized by dementia and periodic complexes on EEG.

Causative drugs: Lithium with Levodopa, Lithium, Lithium with Nortriptyline, Amitriptyline.

Symptoms: Dementia, confusional state, myoclonus, Parkinson's syndrome, dystonia, grimacing, dysarthria, oculogyric crisis, blepharospasm, swallowing difficulties, torticollis and trismus.

Treatment: patients are advised to discontinue the causative drugs. When the patients are treated with high potency antipsychotic drugs a low starting dose is recommended to reduce the risk of acute dystonia compared with a standard dose.[37]

Fetal valproate syndrome (FVS): Valproic acid is a commonly used anticonvulsant and also used in the treatment of bipolar affective disorder. Although, its teratogenic effects are well known, the exact mechanism is unclear which result in multiple birth defects, dysmorphic facies, developmental delay, learning difficulties and/or behavioural problems. Fetal valproate syndrome is the term used to encompass these teratogenic effects.

Causative drug: Sodium valproate.

Symptoms: Neural tube defects, trigonocephaly, radial ray defects, pulmonary abnormalities,

coloboma of iris/optic, low verbal IQ, autism and autistic spectrum disorder.

Treatment: High dose folic acid (4 mg/day) is recommended during pregnancy, starting at least 6 weeks pre-conception and continuing through the first trimester. Folic acid supplements are thought to be protective against malformations, in particular against neural tube defects. Some clinicians are of the opinion that it may be advisable for pregnant women to continue folic acid until delivery, due to the continued development of the fetal brain throughout the pregnancy. Serum α-feto-protein levels in the second trimester may be helpful in picking up open neural tube defects. Antenatal scans should be able to pick up most major malformations, especially if specific attention is being paid towards anomalies known to be associated with FVS.[38] (Fig 7)

Pseudolymphoma Syndrome (PS): PS is a rare form of adverse cutaneous drug reaction.

Causative drugs: Anti-arrhythmic, anti-hypertensive, anti-

psychotic, antibiotic, anti-convulsant, anti-thyroid, anti-inflammatory drugs. It has also been described with biologic drugs (TNF-A antagonist, adalimumab, infliximab, etanercept), α-Interferon and other cytokines.

Symptoms: Fever, cutaneous eruption, lymphadenopathy and hepatosplenomegaly. (Fig 8)

Treatment: Cessation of the causative drug is the management of Pseudolymphoma Syndrome .[39]

Gray baby syndrome (Gray or Grey syndrome/GBS): Gray syndrome is a rare but serious side effect occurs in newborn infants (especially premature babies) following the intravenous administration of the antimicrobial chloramphenicol.

Causative drug: Chloramphenicol.

Symptoms: Vomiting, ashen gray color of the skin, limp body

Fig. 1: Diffuse erythema on the patient's right arm

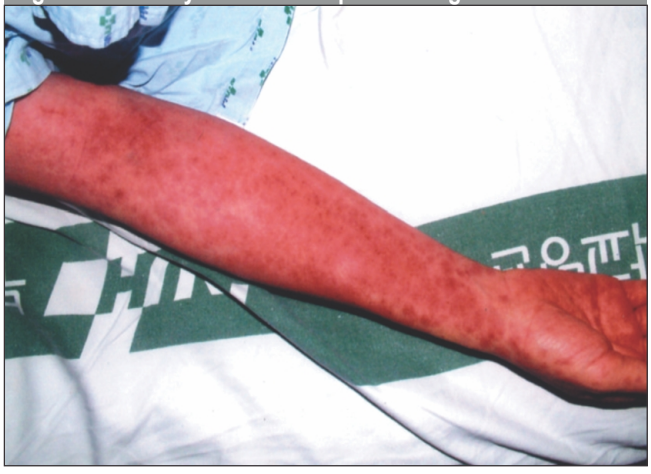


Fig. 2: Blue-gray hyper pigmentation of the face (Blue Gray Syndrome)

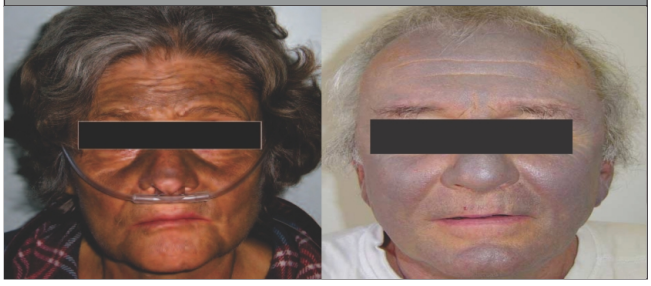


Fig. 3: Patient photography shows erythematous exofoliative maculopapules on the edematous face (A), and polymorphic erythematous maculopapules disseminated on lower legs (B)

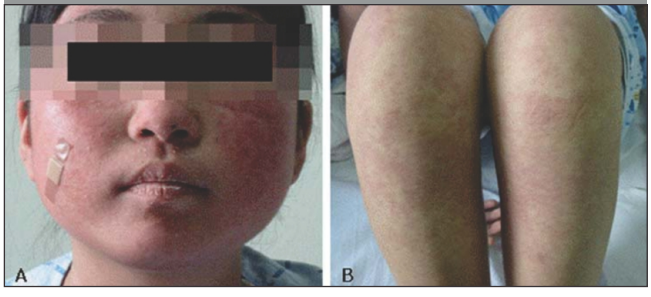


Fig. 4: Cutaneous necrosis

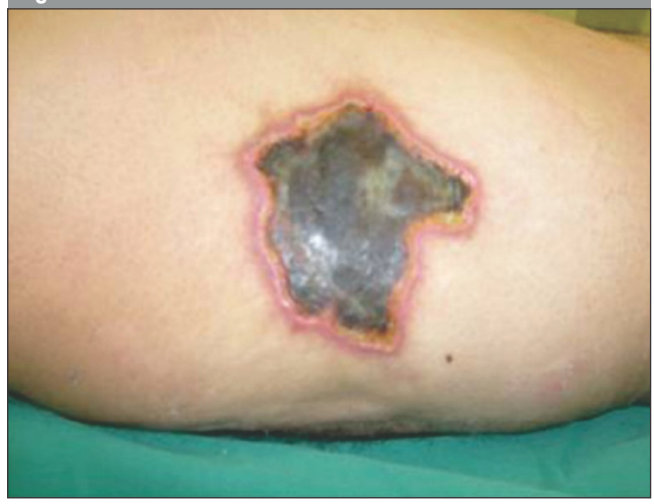


Fig. 6: Dry rash, erythema, blistering and desquamation of the palm

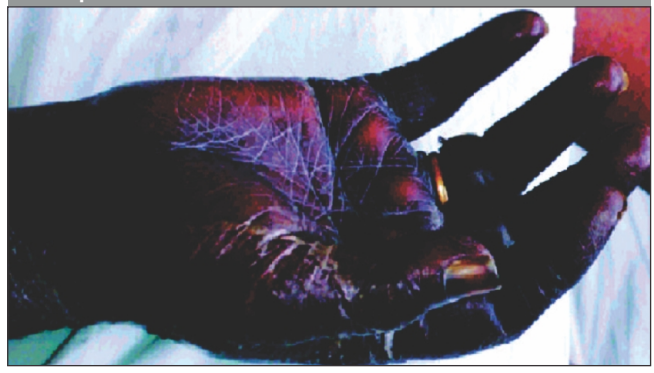


Fig. 5: Erythematous skin lesion

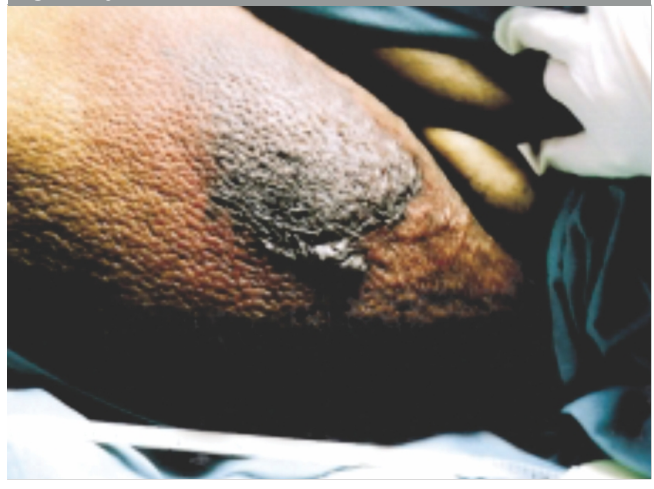


Fig. 7: Examples of major malformations seen in FVS. (i) Repaired neural tube in lumbo-sacral region (ii) Coloboma of the iris (iii) Split hand.

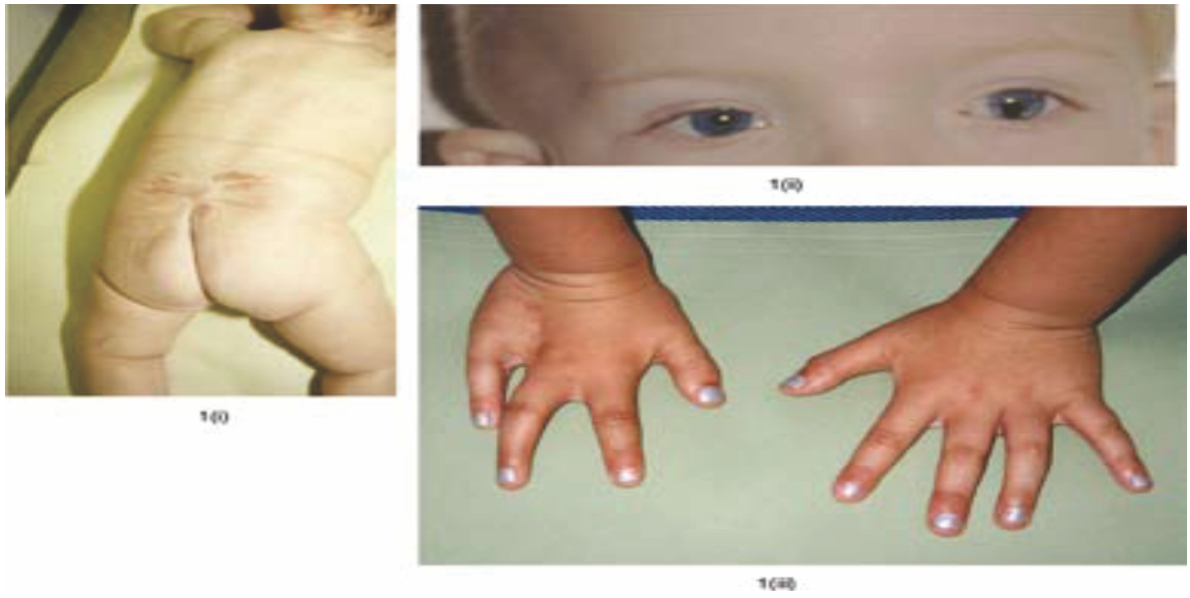
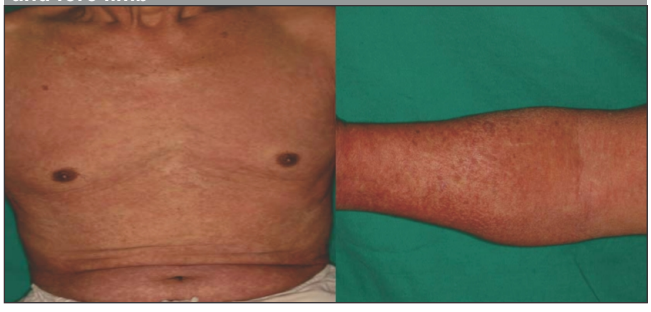


Fig. 8: Generalized maculopapular eruptions on the trunk and fore limb



tone, hypotension, cyanosis, hypothermia, cardiovascular collapse.

Treatment: Chloramphenicol therapy is discontinued immediately. Phenobarbital and third generation cephalosporin effectively can be given at recommended doses.[40]

CONCLUSION

Since last few years there are more reports of the adverse effects induced by the drugs, experts says that additional care is required for the better patient care and also to improve the quality of life. The drug induced syndromes enhances the patient duration of hospital stay and cost of the therapy. The entire health care professional should be aware of the iatrogenic diseases and its management.

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