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**Case Report**

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# A case report of Dapsone Hypersensitivity Syndrome in a child with Lepromatous Leprosy and Potential Genetic Element

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**Abstract**

Dapsone hypersensitivity syndrome (DHS) is characterized by fever, skin rash, eosinophilia, lymphadenopathy, and multi systemic manifestations following Dapsone therapy [1]. The incidence of DHS ranges from 0.5-3% while the time from the commencement of the Dapsone to the onset of symptoms varies from several hours to six months [1]. DHS might lead to irreversible organ damage or fatality if not recognized early and managed appropriately [1]. Genetic component is involved in the pathogenesis of DHS and relatives of the index case are at increased risk of developing similar adverse events following Dapsone [5]. Here, we are going to report a child, who presented with clinical and biochemical features of DHS following Dapsone treatment, given for the management of Lepromatous Leprosy (LL), whose father had also developed similar symptoms suggestive of DHS, while on the treatment for LL.

*Keywords: Dapson, Fever, Skin rash, Multi organ involvement, Lepromatous Leprosy, HLA B*

## INTRODUCTION

Dapsone hypersensitivity syndrome (DHS) is characterized by fever, skin rash, eosinophilia, lymphadenopathy, and multi systemic manifestations following Dapsone therapy [1]. The incidence of DHS ranges from 0.5-3% while the time from the commencement of the Dapsone to the onset of symptoms varies from several hours to six months [1]. DHS might lead to irreversible organ damage or fatality if not recognized early and managed appropriately [1]. Genetic component is involved in the pathogenesis of DHS and relatives of the index case are at increased risk of developing similar adverse events following Dapsone [5]. Here, we are going to report a child, who presented with clinical and biochemical features of DHS following Dapsone treatment, given for the management of Lepromatous Leprosy (LL), whose father had also developed similar symptoms suggestive of DHS, while on the treatment for LL.

## CASE REPORT

A five year nine months old boy, was admitted to the Dermatology ward with a history of high grade intermittent fever of eight days' duration. He was a diagnosed to have LL two months prior to this presentation and on Dapsone, Rifampicin and





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Clofazimine (MTD-multi drug therapy) since the day the diagnosis was confirmed. There were no other systemic symptoms at the time of admission. Two days after admission his mother noticed icterus in the sclera and passage of dark coloured urine. At the same time, he developed episodic, generalized, mild abdominal pain and on and off breathing difficulty. Since the 3rd day of admission he developed abdominal distension, which had progressed over few days. On the 4th day of admission he developed erythematous papular itchy skin rash in both upper limbs which spread all over the body gradually over the next two days' duration. He experienced myalgia and nausea apart from above symptoms. On the 5th day of admission he was transferred to the Paediatric ward for further care.

He was born as the youngest child to nonconsanguineous parents. He had been fit and healthy in the past. His father, 41 years old, had been diagnosed with LL three years before our child was diagnosed with LL and he had been treated with Dapsone, Rifampicin and Clofazimine for few months. He had developed a febrile illness associated with a skin rash while on above drugs and subsequently he was found to have pleural effusion and hepatosplenomegaly. He had been treated with Methylprednisolone for a long period that resulted in complete resolution of the febrile illness. A couple of years after that, he succumbed to death following complications of pulmonary tuberculosis, few days before his son presented with features of LL. This information was given by child's mother as far as she could recall but no documents were available.

On admission to the paediatric ward, the child was jaundiced, febrile, and tachypnoeic. There was bilateral cervical lymphadenopathy, and generalized, diffuse, maculopapular, non-blanching, erythematous rash sparing hands, feet and mucosal membranes. Air entry in the lungs was reduced bilaterally slightly and abdomen was distended with mild hepatosplenomegaly without any free fluid. Rest of the systemic examination remained normal.

His full blood count (FBC) showed significant lymphocytic leucocytosis with increased eosinophil count, while the blood film revealed many reactive lymphocytes with a few atypical lymphocytes, toxic changes in neutrophils and features of low grade haemolysis. His liver functions showed moderately elevated transaminases, conjugated hyperbilirubinemia, while renal functions remained within the normal limits. Sonographic examination confirmed hepatosplenomegaly with bilateral small pleural effusions with normal hepatobiliary system. His chest x-ray was normal apart from small pleural effusions. His glandular fever screening was negative, erythrocyte sedimentation rate (ESR) was normal for the age and all the cultures were negative.

Initially he was commenced on broad spectrum intravenous (IV) antibiotic empirically as he presented with high fever with raised inflammatory markers. Despite that the temperature continued to spike with further deranged in biochemical parameters. On the ground of the clinical picture of multi system involvement, which coincided with the commencement of Dapsone, DHS was entertained as the diagnosis. Then Dapsone was discontinued and he was commenced on IV Hydrocortisone. With steroid his fever started to settle initially and other symptoms and signs improved gradually along with biochemical markers subsequently. Later he was switched to oral Prednisolone and discharged with a plan of tapering the drug over six weeks and reviewing in the paediatric outpatient and dermatology clinics. During the follow up visits he showed remarkable improvement in his clinical and biochemical parameters. His rash had disappeared without desquamation. Five weeks after the onset of symptoms, he was completely asymptomatic and all the biochemical parameters were within the normal range.

## DISCUSSION

DHS is a hypersensitivity response to Dapsone which is used mainly as an anti-inflammatory and antibacterial agent for the treatment of various infectious, immunological and hypersensitivity disorders [1].

The adverse effects of Dapsone are categorized in to two types as [5]

1.) Dose-dependent (pharmacological) - haemolytic anaemia, methemoglobinemia
2.) Dose-independent (idiosyncratic) – skin hypersensitivity reactions and DHS [1]

The reported incidence of DHS varies from 0.5-3%. The median time gap between the initiations of the Dapsone to the onset of symptoms can be ranged from several hours to 6 months [1]. DHS is characterized by fever, skin rash, eosinophilia, lymphadenopathy, hepatic, pulmonary, and other systemic manifestations following Dapsone therapy [1, 2, 5]. Moreover, DHS is said to be having a classic triad including fever, skin eruption and multi organ involvement [1]. DHS can evolve in to irreversible organ damage or fatality if not recognized early and managed accordingly [1]. Genetic factors have been recognised in the pathogenesis of DHS and relatives are at higher risk of developing similar adverse effects following exposure to Dapsone. Recent studies have shown that there is an association between DHS and the presence of HLA B * 13:01 and the presence of one locus within the major histocompatibility system (MHC) as a risk factor and predictor of DHS [1, 4, 5]. Presence of HLA B * 13:01 allele was recognized as a predictor and a risk factor of DHS among the Chinese population initially [4]. However, HLA B * 13:01 has been shown in several other studies in Asia as a strong predictor for DHS.

Manifestations of DHS include high grade fever, skin rash, lymphadenopathy, eosinophilia, atypical lymphocytosis, hepatitis, acute pneumonitis, neurological, and other systemic features of multi-organ involvement. Liver involvement displays a mixed hepatocellular and cholestatic pattern [1, 2] and drug induced cholangitis [2] has been reported in patients with DHS [2]. DHS has been considered as a manifestation of DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms), which is caused by several drugs including anticonvulsants, Sulphonamides, Allopurinol and Minocycline [1, 2]. Skin manifestations reported in DHS include erythroderma, exfoliative dermatitis, papular erythematous, pustular eruptions, erythema multi-forme, Stevens-Johnson syndrome and toxic epidermal necrolysis. [1]. Acute Pneumonitis (eosinophilic pneumonia) with hypoxia and pleural effusion has been reported as pulmonary involvement [1].

Pathogenesis of DHS is not very well established. However, proposed mechanism include formation of haptens by metabolites of Dapsone with the subsequent production of anti-Dapsone antibodies. The suggested mechanism of haematological toxicity include inter-individual variability in the metabolism of Dapsone by N-hydroxylation to hydroxylamine by hepatic microsomal P-450 system [3].

The diagnosis is based on the presence of fever, skin rash, and systemic manifestations in the background of exposure to Dapsone [1, 2]. According to Richardus and Smith diagnostic criteria include [5]

1.) Presence of at least two of: fever, skin eruption, lymphadenopathy, and liver abnormalities (hepatomegaly, hepatitis, jaundice, and/or deranged liver function tests)
2.) Symptoms manifesting within 2 to 8 weeks of starting therapy and resolving after withdrawal of the drug
3.) Symptoms are not attributable to any other drug used simultaneously or to lepra reactions
4.) Symptoms unrelated to any underlying disease
Management of DHS include prompt withdrawal of Dapsone, commencement of oral or parenteral glucocorticosteroid [1]. Other measures include volume replacement, nutritional support, antibiotic, and skin care. Longer duration of weaning off steroid is indicated as Dapsone may remain in the body up to 35 days [1].

Patients who are on Dapsone for various indications need to be closely followed up clinically for the development of DHS with a high index of suspicion to arrive at an early diagnosis. The prompt withdrawal of the drug, administration of glucocorticosteroid, and other supportive management lead to rapid recovery [1]. Delayed withdrawal of Dapsone can result in devastating consequences and potentially fatal effects due to multi organ dysfunction.

Our child presented with high grade fever after about two months of starting Dapsone. Subsequently he developed skin rash, cholestatic

jaundice, lymphadenopathy, pulmonary involvement, and hepatosplenomegaly. His laboratory investigations revealed eosinophilia, haemolysis, atypical lymphocytosis, and hepatobiliary involvement in the form of transaminitis and conjugated hyperbilirubinemia. His symptoms, signs, and biochemical markers settled gradually with discontinuation of Dapsone and the commencement of steroid. His father also had developed the same symptoms while on Dapsone and this suggests the involvement of genetic factors. Unfortunately, we could not proceed with investigations to confirm the genetic link as his father has passed away due to complications of pulmonary tuberculosis..

**Author declaration**
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**Author contributions:**
All authors were involved in the management of the patient. Weerasekara S.P.N. did the literature review and drafted the manuscript. All the authors except Dr.Chintha Abeynayake have read and approved the manuscript.

**Data availability:**
All necessary data and references are provided

**Conflict interest:**
Authors declare no conflict interest.

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