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# PREGABALIN INDUCED HYPERSENSITIVITY REACTION AND JOINT PAINS IN PATIENT WITH LUMBOSACRAL RADICULOPATHY

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## ABSTRACT

Pregabalin is an antiepileptic medication commonly used for other purposes. It is also approved for neuropathic pain. Reported adverse effects are not severe, short lasting and are usually well tolerated<sup>1</sup>. The most common side effects comprise of lightheadedness, sedation, double vision, increase in bodyweight and imbalance whereas decrease in neutrophil count and hypersensitivity are the uncommon adverse effects. In the literature till date, few case reports are available on the drug reactions to pregabalin. We report a case of young female who developed hypersensitivity reaction with pregabalin including body rashes, hives peripheral edema, and joint pains. Using the Naranjo Adverse Drug Reaction Probability Scale, a “probable” reaction (Score: 7) was attributed to our patient. Clinicians should keep in mind the reported side effects and counsel patient about the possible side effects before starting it with regular follow up of patients for side effects monitoring.

**KEY WORDS:** Pregabalin, hypersensitivity reaction, drug induced arthritis, neuropathic medication, lumbosacral radiculopathy pharmacological management, drug induced urticarial rash

## INTRODUCTION

Pregabalin is a frequently prescribed medication for neuropathic pain and generalized anxiety disorder<sup>1</sup> with occasional use as antiepileptic medication<sup>1</sup>. Throughout the dorsal spinal cord and brain, gabapentin and pregabalin binding sites are present. It is Gamma-aminobutyric acid (GABA) analogue which acts as an inhibitory neurotransmitter. Pregabalin decreases excitatory neurotransmitter release in central nervous system which is responsible for pain pathways and epileptogenesis. Reportedly,  $\alpha\delta$  subunit of presynaptic P/Q-type Calcium channels facilitates its action by ultimately decreased  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) activation on noradrenergic nerve endings<sup>1, 2, 3</sup>. Moreover, concentration of many neurotransmitters including substance P, glutamate, serotonin, dopamine, and noradrenaline are also decreased<sup>4</sup>.

Reported elimination half-life of pregabalin is 5.5 to 6.7 hours. It is exclusively excreted through kidneys with little hepatic metabolism. Daily effective dose is

300-600mg, but lower doses are also effective in many cases. Dizziness and somnolence are the most frequent which are usually mild and short lasting<sup>1</sup>. Other common side effects are double vision, increase in bodyweight and balancing problems while reduced neutrophil count and hypersensitivity are uncommon ranging from 1 out of 100 to 1 in 1000 patients<sup>5</sup>. Pregabalin is a precursor of gabapentin with similar effectiveness in diabetic peripheral neuropathy secondary to diabetes, post herpetic neuralgia and focal epilepsy<sup>6,7,8</sup>. Side effect profile of pregabalin is more favourable than gabapentin justifying its increased use nowadays. Unfortunately, few case reports are published on drug reaction to pregabalin.

A case report of urticarial rash due to pregabalin and fall in neutrophils count in a kidney transplant recipient was published in 2019 in BMC nephrology journal<sup>9</sup>. Pregabalin-induced rash was rarely reported in Phase 3 clinical trials, and there are few available reports on the development of a rash due to pregabalin. In our case report, pregabalin was discontinued as soon as the patient complaint of rashes, within 1 week of starting

the drug .There was less possibility of any significant withdrawal effects. It is recommended to taper the doses over 1 week duration if the patients are on pregabalin for long time. Still few health care professionals keep its side effects in mind while prescribing it to the patients and inform patient properly. Our aim of writing this case report is that the patient should be counselled about the side effect which can lead to morbidity and sometimes even mortality due to anaphylactic reaction if not diagnosed and managed on time. Pathogenesis of rashes caused by pregabalin is not clearly understood. Recommended practice is to start low doses of pregabalin and escalate gradually which may reduce the incidence of side effects<sup>10</sup>. Informed written consent of patient was taken before writing the case report.

### CASE

A 30-year-old female patient, house maid, mother of 3 children, presented to the neurology clinic with complaint of lower backache radiating to lower limbs with occasional numbness of her feet. There was no history of trauma or weightlifting. Bowel and bladder were unaffected. On the examination, There was no sensory level .Pin prick sensation were reduced in lumber L4,L5, sacral S1 dermatome bilaterally. Temperature, vibration, and proprioception sensation were intact. No motor weakness was found in proximal and distal muscles. Straight leg raising test was restricted to 60 degrees. Bilateral knee jerks were normal, but ankle reflexes were diminished bilaterally. She had no significant past medical or surgical history. No history of known allergy to any medication or food. No history of fever, body rashes, joint pains, or edema. Her backache on pain analogue scale was 7/10. She did not receive any medication for her back pain except for combination of acetaminophen and orphenadrine with the partial relief in her symptoms .She was prescribed pregabalin 75 mg at night along with acetaminophen and orphenadrine on as per need basis. Back care and physiotherapy for lumbosacral radiculopathy was advised with follow up after 2 weeks. After 4 days, patient again visited our neurology clinic with complaints of itching and rashes all over body more marked on trunk and lower limbs (FIGURE 1-3 ) while hives were present on her forehead ,scalp, and face .(FIGURE4 ) No mucosal lesions were present. Her both hands were edematous (FIGURE 5-6 ), and she had pain and tenderness over elbow, knees, and ankles bilaterally without joint swelling, warmth, or redness.

She said to have these complaints after having 3rd



**FIGURE 1: ERYTHEMATOUS RASHES ON THE LEFT THIGH OF PATIENT**



**FIGURE 2: RASHES ON ARM**



**FIGURE 3 : HIVES AND RASHES ON FOREHEAD**



**FIGURE 4: ERYTHEMA AND REDNESS OF HANDS LEFT THIGH OF PATIENT**

dose of pregabalin and she thus stopped it. Pregabalin was stopped immediately. She was prescribed antihistamine injection pheniramine maleate (Avil 25 mg ) and injection Decadron 4 mg stat , followed by tablet cetirizine (Zyrtec 10 mg ) 3 times daily. She was also advised blood work up to rule out any underlying causes including CBC. Hemoglobin 10.6 g/dl normocytic, normochromic, platelet 441 per cmm,TLC 9.3 per cmm, ESR 42 mm/1st hr ,CRP normal.ANAProfile was negative URIC ACID 4.0 mg %, anti CCP negative (<0.5 U/ml) .After 1 week she was followed again in the clinic and showed complete resolution of all rashes, edema, and joint pains.

## DISCUSSION

Our case report emphasizes the significance of careful monitoring of drug side effects profile before prescribing it to patients along with regular follow up. Pregabalin is being frequently used for treating neuropathic pain. Numerous factors are proposed regarding increased chances of an individual to develop a drug-induced rash. These include woman of child-bearing age as in our case, the starting dose, co-existing viral illness, autoimmune disorders, pharmacological changes, and age of patient.<sup>11,12</sup>

To determine whether an adverse drug reaction was due to the drug instead of other factors, we decided to use The Naranjo Adverse Drug Reaction Probability Scale which has been used in literature<sup>13</sup>. 10 parameters are presented as questions including the relationship between drug administration and occurrence of event, any other causes for the event, drug levels, dose – response relationships and patient's previous response of the medication. The drug-drug interactions are not included in this scale. The points are cut if another factor may be responsible for the adverse event while evaluating drugs individually for causality, thus weakening the causal association. Score are termed as definite, probable, possible or doubtful<sup>14</sup>. In our case it turned out to be a "probable" reaction (Score: 7).

The most frequently encountered drug-induced rash is erythematous resulting from delayed cell-mediated hypersensitivity. First or second week of therapy is the usual time duration<sup>13</sup>. There was a significant reduction of the mentioned lesions which were seen in our patient after the drug was stopped along with timely administration of symptomatic medications. 2 days after starting pregabalin, rashes appeared in the case reported by Smith et al<sup>15</sup>. Three large randomized controlled trials checked the risk and effectiveness of pregabalin in neuropathic patients. Pregabalin was found to be well tolerated in a six-week study on 246 patients receiving 150 mg, 600 mg, or placebo.<sup>16</sup> Light-headedness and sleepiness were the most

common adverse effects. Similar adverse effects were reported by two other large clinical trials.<sup>17,18</sup> A randomized, double-blind, placebo-controlled trial also showed good tolerance of pregabalin (600 mg/day) with peripheral oedema, light-headedness, increase in bodyweight and sleepiness as common adverse effects.<sup>19</sup>

In our patient in addition to erythematous and urticarial rashes, peripheral oedema and multiple joint pains were also present. The cause of peripheral oedema due to the gabapentinoids is not known, but it is common. 7.6 % patients develop peripheral oedema as compared to 0.4% of patients on placebo therapy. Other literature reported Joint swelling in (1.9%) patients. This adverse effect resulted in 0.5% of pregabalin-related discontinuations in clinical trials compared with 0.2% of patients receiving placebo. There is no association between peripheral oedema and cardiovascular complications (hypertension or congestive heart failure), or with deteriorating kidney or liver function<sup>20</sup>. Our patient also developed oedema of hands as seen in the pictures without any symptoms or signs of cardiovascular or hepatic dysfunction.

5.2 % of older patients develop rashes as compared to usual range of 0.3% to 1.3%<sup>22</sup>. The troublesome form of rash is a severe purpuric, vesiculobullar rash that may evolve into Stevens–Johnson syndrome. Joint pain occurs as a side effect in 6% of people.

## CONCLUSION

Although Pregabalin is thought to be an effective medication with frequently tolerable adverse effects, vigilant monitoring of patients is needed. It is being increasingly prescribed recently by neurologists, psychiatrists, and general practitioners. All health care professionals should keep in mind the reported side effects and counsel patient about the possible side effects. Further research is needed regarding its pathogenesis of hypersensitivity, pharmacology, and safety parameters of pregabalin.

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**Dr. Ramla Nayaib Hashmi;** Manuscript writing, literature search, case data collection, manuscript revision.

**Dr. Iqra;** case data collection, manuscript revision.

**Dr. Ummul Kiram;** literature search, manuscript writing and revision.

**Dr. Sobia Shakeel;** literature search, references

**Dr. Tamaniat;** manuscript revision, references.