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*Review Article*

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# Evaluation of PSA, Prostatic Acid Phosphatase, Calcium and Magnesium in Case of Benign Prostatic Hyperplasia (BPH)

**SS Haque[1], Md. Nasim Akhtar[2], Rekha Kumari[3]**

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**Abstract**

Benign prostatic hyperplasia **(**BPH) is the most common pathology of the prostate gland in men. Raised levels of PSA are seen in different pathological conditions involving the prostate. PAP levels are altered in inflammatory, infectious or abnormal growth of the prostate tissue. Serum calcium and magnesium levels were also found to be altered in prostate cancer and BPH. The present study was carried out to study the levels of PSA, Prostatic Acid Phosphatase (PAP), calcium, and magnesium in serum of patients with BPH and to evaluate the relationship between them as well.

**Keywords:** Benign prostatic hyperplasia **(**BPH); Prostatic Acid Phosphatase (PAP); Serum.

## Introduction

Benign prostatic hyperplasia (BPH), also called benign enlargement of the prostate (BEP or BPE), is a noncancerous increase in size of the prostate, a common condition in men above 50 years. On histological evaluation, it shows hyperplasia of prostatic stromal and epithelial cells, resulting in the formation of large, fairly discrete nodules in the transition zone of the prostate.[1] BPH is an androgen-dependent process, the modifiable and non-modifiable risk factors for BPH include age, genetics, hormones, metabolic syndrome, obesity, diabetes, and chronic inflammation. Clinical manifestations of BPH are caused by extrinsic compression of the prostatic urethra leading to impaired voiding. Chronic inability to completely empty the bladder may cause bladder distension with hypertrophy and instability of the detrusor muscle.[2,3] Some patients with BPH present with hematuria. Because the severity of symptoms does not correlate with the degree of hyperplasia, and other conditions can cause similar symptoms, the clinical syndrome that often accompanies BPH has been described as lower urinary tract symptoms. PSA an important tumor marker that predicts the clinical progression and response to medical therapy in patients with BPH thus help in selecting the regimen for medical treatment.

Prostate specific antigen (PSA) is a 237-amino acid monomeric serine protease and 33 kilodalton glycoprotein produced in prostate epithelial cells

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and it is first identified by the Wang et al.[4] Its normal physiologic role is as a liquefying agent for seminal fluid; only a tiny amount leaks into the blood, therefore its normal serum level is usually very low. Elevated serum levels of PSA have been associated with prostate carcinoma. Men above 45 years are prone to BPH, a universal phenomenon which increases with age. It has shown considerable promise and has been acclaimed the best marker for prostate malignancy in recent years, although its plasma concentration also increases in BPH, but to a lesser extent. The reduced specificity of the two markers is further complicated by a number of pathological factors like prostatic infarct, acute bacterial prostatitis as well as acute urinary retention or digital rectal examination (DRE).[5,6]

Prostate specific antigen can exist in the serum in two forms:

Total PSA (tPSA) is a predominantly complexed to protease inhibitors bound/complexed (to serum protein) widely used tumour marker for the early detection and monitoring of patients with prostate cancer. One of the drawbacks of tPSA is the appreciable false-positive results. Manipulations of the prostate gland, benign conditions, such as BPH and clinical or subclinical prostatitis, have been reported to contribute to tPSA elevations.[7] These benign causes of elevated serum tPSA can create a diagnostic dilemma in prostate cancer detection programmes that use serum PSA only as a screening test.

Free PSA (fPSA) is not bound to these proteins. For unknown reasons, the percentage of fPSA (f/tPSA) is lower in serum from patients with prostate cancer than from patients with a normal prostate or benign disease. Preliminary examination suggests that a lower f/tPSA is more reliable and can reduce unnecessary biopsies in patients being evaluated for prostate cancer; elevated levels of fPSA are associated with benign prostatic hyperplasia (BPH). Measuring the different forms of PSA may help to discriminate between prostate cancer and benign diseases.[8]

Early detection and treatment in asymptomatic men may improve the mortality rate and the quality of life. Screening for markers such as prostate specific antigen (PSA) and prostate acid phosphatase (PAP) resulted in detection and treatment of the disease at an earlier stage. Men of 50 years of age or above without any family history of cancer and those at 40 years of age with family history must undergo digital rectal examination (DRE) and PSA levels should be checked annually as recommended by of American Urological Association (AUA) and Food and Drug Administration (FDA).

Prostatic acid phosphatase (PAP) is an enzyme produced by several types of tissue, including normal prostate tissue and it is secreted by prostate columnar epithelium secretory cells following puberty. PAP emerged as the world's first clinically useful tumor marker in the 1940s and 1950s. With the introduction of the PSA test in the 1980s, which performed significantly better than PAP in terms of screening and monitoring response to treatment, PAP fell into disfavor. Prostatic acid phosphatase (PAP), a sialoglycoprotein with a molecular weight of 100,000[9] has been used for early screening and detection of prostate carcinoma in high risk group [10,11], although its role in staging the carcinoma has been doubtful.[12,13] There are two forms of PAP, including the cellular form (cPAP, highly expressed in the prostate cells) and the secretory form (sPAP, expressed only in the prostate and is mostly released into seminal fluid),[14] with different isoelectric points and molecular weights.[15] Apart from different biomarker, trace elements such as Calcium (Ca) - magnesium (Mg) are essential to normal human homeostasis, results in a number of clinical complications including BPH. Suggested processes implicated in the progression of prostate disorders are from oxidative stress, to cellular senescence.[16,17]

One of the hypotheses suggests that a high intake of protein or calcium from dairy products may enhance the risk for prostate cancer hence calcium considered as the probable cause of prostate cancer and BPH. Conversely, high magnesium intake can reverse calcification damages and inflammation, if used intensely. As the physiology suggests an antagonistic effects of magnesium over calcium on our body and as a rule in general, the more rigid and inflexible our body structure, the less calcium and the more magnesium we need**.** There is reasonable evidence to suggest that calcium may play an important role in the development of prostate cancer," says Dr. Carmen Rodriguez, senior epidemiologist in the epidemiology and surveillance research department of the American Cancer Society (ACS). Several epidemiologic studies sustain the role of calcium in prostate cancer showed an increased risk for advanced or fatal prostate cancer among men whose diets are unusually high in calcium.[18] Both normal and cancerous prostate cells possess the calcium-sensing receptor, a G-protein coupled receptor that is activated by extracellular calcium[19] and also they express calcium-dependent channels that regulate

cell proliferation via the control of calcium entry into the cells.[20] Calcium and magnesium levels in the body are jointly regulated through a negative feedback system.[21] Magnesium (Mg) is an essential micronutrient for humans and plays many important roles in the function of over 300 enzymes and it is the second most abundant intracellular cation in the body.[22] At the extracellular level, an increase in $Ca^{2+}$ or a decrease in extracellular $Mg^{2+}$ further increased $Ca^{2+}$ influx. The efflux control of Ca and Mg is regulated by a melastatin-like transient receptor potential (TRPM). These are a diverse group of voltage-independent $Ca^{2\pm}$ permeable cation channels present in mammalian cells. TRPM6/7 gene mutations have been demonstrated in hereditary hypomagnesaemia caused by $Mg^{2+}$ reabsorption impairment.[23] Additionally, other studies have shown $Mg^{2+}$ entry preference over $Ca^{2+}$. However, in the absence of $Mg^{2+}$, the channels are able to conduct $Ca^{2+}$ currents, which ultimately increases in extracellular $Ca^{2+}$ or a decrease in extracellular $Mg^{2+}$ increases $Ca^{2+}$ influx. Additionally, the subsequent increase in the $Ca^{2+}/Mg^{2+}$ ratio and TRPM7 expression has been demonstrated in age-matched prostate cancer patients. Therefore, an increase in the serum $Ca^{2+}/Mg^{2+}$ ratio will increase $Ca^{2+}$ entry by the activation of TRPM7 channels, which eventually leads to increased cell proliferation and cancer formation.[24] High Ca/Mg ratio levels were associated with risk of prostate cancer. Mg levels were significantly lower among men with high-grade prostate cancer, particularly among men with high blood Ca levels. These findings suggest Mg interacts with Ca to affect prostate cancer risk. This provided evidence of the Ca/Mg hemostasis and its involvement in cell proliferation as well as prostate cancer development. The tight regulation of this channel has also been attributed to theTRMP7 gene and the Ca/Mg ratio has also been demonstrated in clinical studies of prostate cancer but not in case of BPH, so further studies are required.

## Discussion

PSA is a serine protease enzyme produced by normal prostate cells and plays an important role in fertility. In men with prostate cancer there seems to be a lower proportion of fPSA and this has been expressed as a decrease in the f/t PSA ratio. The reasons for this are not fully understood. Studies in 1991 demonstrated that there is a higher proportion of PSA bound to Alpha-1-antichymotrypsin (ACT) in prostate cancer.[25,26] In human serum PAP is a secreted glycoprotein (100 kDa) enzyme is synthesized in the prostate gland's epithelial cells was widely studied as a surrogate marker for prostate cancer until the establishment of prostate-specific antigen (PSA) as the new standard.[27] PSA and PAP considered as potential biomarker and has a significantly higher correlation with the morphological characteristics of prostate cancer and can provide a more important in the diagnosis and prognosis than any other markers currently available.

Mg has an effect on a variety of cell membranes through a process involving Ca channels and ion transport mechanisms. Mg is therefore responsible for the maintenance of the trans-membrane gradients of sodium and potassium.[28] Ca reabsorption is truncated when Mg is adequately reabsorbed. It has been shown that Ca reabsorption is not altered in Mg deficiency; however, elevations of extracellular Mg results in a specific inhibition of Ca reabsorption within the loop of Henle.[29] The Ca/ Mg ratio play an important role in the initiation or progression of the disease remains doubtful and requires further studies.

## Conclusion

PSA may be elevated more frequently than PAP in some patients with BPH, in combination, indicates either prostatitis or Prostate cancer and rules out BPH. The calcium level is also low in BPH patients which ultimately affect the Ca/Mg ratio.

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*Review Article*

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# Phenylketonuria (PKU): An Inborn Metabolic Disorder

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**Abstract**

During process of digestion, proteins are broken down in into amino acids. Mainly the proteins contain 22 standard amino acids and several non-standard amino acids. We possess synthetic pathways for only 11 amino acids out of 22 standard amino acids. The remaining ones must be obtained from diet and hence they are referred to as essential amino acids. During day to day protein turnover most of amino acids used in protein synthesis were not from food but obtained through endogenous protein breakdown. The amino acid degradation occurs in Liver, Muscles and Kidneys. The liver being the major site of degradation while for some specific ones Muscles and Kidneys are the sites. During the amino acid degradation the nitrogen is removed from the carbon skeleton and transferred to the alpha-ketoglutarate which results into Glutamate. The carbon skeletons are converted into intermediates of mainstream carbon oxidation pathways via specific adapter pathways. Surplus nitrogen is removed from glutamate, and excreted in urea. In the degradation process, the amino acids are converted into the intermediates of the citric acid cycle to pyruvate which in turn can serve as precursors for gluconeogenesis, can be referred as *glucogenic* amino acids. Those amino acids which yield acetoacetate are termed as *ketogenic*.[1] Phenylketonuria (PKU) is a metabolic disorder occurring since birth which results into decreased metabolism of the amino acid phenylalanine.[2] It is observed that the untreated, PKU can develop intellectual disability, seizures, behavioral problems, and mental disorders.[3] It may also result in a musty smell and lighter skin. A baby born to a mother who has poorly treated PKU may have heart problems, a small head, and low birth weight.[2] Present review study will compare the prevalence of disease in the countries with special focus to India.

**Keywords:** Amino acids; Phenylketonuria (PKU); Metabolism; Phenylalanine.

## Introduction

During process of digestion, proteins are broken down in into amino acids. Mainly the proteins contain 22 standard amino acids and several non-standard amino acids. We possess synthetic pathways for only 11 amino acids out of 22 standard amino acids. The remaining ones must be obtained from diet and hence they are referred to as essential amino acids. During day to day protein turnover most of amino acids used in protein synthesis were not from food but obtained through endogenous protein breakdown. The amino acid degradation occurs in Liver, Muscles and Kidneys. The liver being the major site of degradation while for some specific ones Muscles and Kidneys are the sites. During the amino acid degradation the nitrogen is removed from the carbon skeleton and transferred

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to the alpha-ketoglutarate which results into Glutamate. The carbon skeletons are converted into intermediates of mainstream carbon oxidation pathways via specific adapter pathways. Surplus nitrogen is removed from glutamate, and excreted in urea. In the degradation process, the amino acids are converted into the intermediates of the citric acid cycle to pyruvate which in turn can serve as precursors for gluconeogenesis, can be referred as *glucogenic* amino acids. Those amino acids which yield acetoacetate are termed as *ketogenic*.[1] Phenylketonuria (PKU) is a metabolic disorder occurring since birth which results into decreased metabolism of the amino acid phenylalanine.[2] It is observed that the untreated, PKU can develop intellectual disability, seizures, behavioral problems, and mental disorders.[3] It may also result in a musty smell and lighter skin. A baby born to a mother who has poorly treated PKU may have heart problems, a small head, and low birth weight.[2] If we go in detailed scenario of PKU, it is evident that the PKU is an autosomal recessive genetic disorder resulting from a mutation in hepatic phenylalanine hydroxylase gene. This mutation further makes phenylalanine hydroxylase enzyme non-functional. Phenylalanine hydroxylase is the enzyme that is necessary for the conversion of the amino acid phenylalanine (Phe) to the amino acid tyrosine. As the Phenylalanine is a large, neutral amino acid (LNAA), which can compete for transport across the blood – brain barrier (BBB) via the large neutral amino acid transporter (LNAAT). Hence the untreated cases of can develop complications like mental retardation, seizures, and other serious medical problems. Therefore, PKU is commonly included in the newborn screening panel of most countries, with varied detection techniques. The mainstream treatment for classic PKU patients is a strict PHE-restricted diet supplemented by a medical formula containing amino acids and other nutrients.[4]

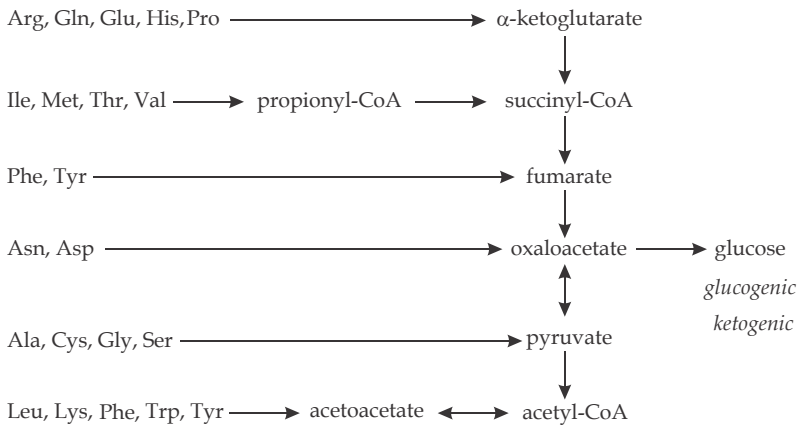


**Fig. 1:** Amino acid breakdown pathways join mainstream carbon utilization at different points of entry
(alanine – ala, arginine – arg, asparagine – asn, aspartic acid – asp, cysteine – cys, glutamine – gln, glutamic acid – glu, glycine - gly, histidine – his, isoleucine – ile, leucine – leu, lysine – lys, methionine – met, phenylalanine – phe, proline – pro, serine – ser, threonine – thr, tryptophan – trp, tyrosine – tyr, valine - val)

This disease is an example of non-allelic genetic heterogeneity. The PAH gene is located on chromosome 12 in the bands 12q22–q24.1. It is shown that more than 400 disease-causing mutations have been found in the PAH gene. PAH deficiency causes a spectrum of disorders, including classic phenylketonuria and hyperphenylalaninemia (a less severe accumulation of phenylalanine). As PKU is an autosomal recessive genetic disorder, both parents must have at least one mutated allele of the PAH gene. The child must inherit both mutated alleles, one from each parent.[4]

**Historical Perspective of PKU**

The disease PKU was first described by a Norwegian physician Asbjørn Følling in 1934.[8] He observed 10 children who were excreting large amount of phenylpyruvic acid in their urine. An interesting story was there behind his findings of PKU, when a mother of two mentally retarded children came to see Følling and informed her children is not only retarded but their urine had a peculiar smell. Følling in his usual thorough way examined children's urine with all routine

methods including ferric chloride test for ketones. Normally, it is brown and turns purple in the presence of ketones. But it turned green in the case of these two children. Følling repeated the test for a few days and was convinced it is indeed not an artifact but the children are excreting something that normal people do not, and he later detected it to be phenylpyruvic acid when the compound on processing smelt like benzoic acid and he called the disease oligophrenia phenylpyruvica, which later came to be known as phenylketonuria (PKU). Jervis described the enzyme defect and the Canadian physician Robert Guthrie who had an affected son and niece devised the newborn screening test.[9]

**Treatment**

The treatment mainly focused on diet with no phenylalanine and other nutrients. In the United States the current recommendation this diet need to be maintained for whole life. It is observed that if patients follow strict diet can live normal life with normal mental development. However, recent research suggests that neurocognitive, psychosocial, quality of life, growth, nutrition, and bone pathology are slightly suboptimal.[4]

**Detection**

Most babies in developed countries are screened for PKU soon after birth. Screening for PKU is done with bacterial inhibition assay (Guthrie test), immunoassays using fluorometric or photometric detection, or amino acid measurement using tandem mass spectrometry (MS/MS). Measurements done using MS/MS determine the concentration of Phe and the ratio of Phe to tyrosine, both of which will be elevated in PKU.[4]

***Guthrie test:*** It is a simple screening blood test for phenylketonuria (PKU). The Guthrie test was the original impetus to newborn metabolic screening. The history of development of test has interesting story that in 1958–59 Dr. Robert Guthrie (1916–95) was asked if he might to develop a simple method to monitor the blood phenylalanine (Phe) level. He developed a test in 3 days. It was a "bacterial inhibition assay."In this test a spot of blood placed on a filter paper disc on surface of agar plate which contains substance inhibiting growth of bacteria. The inhibition can overcome by the presence of high phenylalanine concentration. After incubating the agar plate overnight, the diameter of the growth zone around the test disc is compared to that of a control disc of blood serum to which a known quantity of phenylalanine (Phe) has been added. This permits one to estimate the amount of phenylalanine (Phe) in the test disc.

Bob Guthrie used a common, standardized strain of soil bacterium, *Bacillus subtilis*. The inhibitor was -2-thienylalanine, which inhibits the growth of *B. subtilis*, an effect that was relieved by phenylalanine (Phe). Guthrie's original agar dish was a Pyrex baking pan. Guthrie went on to develop bacterial inhibition assays for other inherited disorders of metabolism, including maple syrup urine, galactosemia, maple syrup urine disease and homocystinuria. These assays are simple, inexpensive, and suited to screening large numbers of individual specimens. The three main laboratory methods now used in the US are the Guthrie bacterial inhibition assay (BIA), fluorometric analysis, and tandem mass spectrometry. Each of these methods can reliably detect PKU.[5]

***Prevalence of Phenylketonuria in the World special focused to India:***

In India the prevalence of the Phenylketonuria is less as compared to rest of countries. Appaji Rao during screening of 172,369 newborns in Bangalore, detected six cases of PKU (1 in 28728 screened).[6] Kaur et al.[7] while screening for PKU, 4451 cases for inborn errors of metabolism in Delhi and detected PKU in 4 (0.08%) cases.

**Conclusion**

The various countries like Saudi Arabia, United States of America, United Kingdom are more affected from occurrences of PKU. In India there are few studies for screening of this disease. These studies show less occurrences of this disease in India. Still there is need for the in-depth study epidemiologically in whole country to understand the quantum of the problem. Public and Government need to have equal participation for the screening studies for detection of PKU. There is chance of more better and healthy life of PKU patients if disease diagnosed early.

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*Review Article*

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# Guillain-Barré Syndrome (GBS): Attack of Self Immune System to the Peripheral Nerves

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**Abstract**

Guillain-Barré syndrome (GBS) is referred to a rare condition in which a person's self-immune system attacks his own peripheral nerves. The disease was first detected by the French physician Jean-Baptiste Octave Landry in 1859. After this during 1916, Georges Guillain, Jean Alexandre Barré, and André Strohl also confirmed the disease onset in some soldiers. The disease can affect the people of all ages but more common in adult males. The disease has recovery, if treated. In case of severity which is rare can lead to total paralysis. Guillain-Barré syndromecan adversely affect the nerves that control muscle movement, transmit pain, temperature, feeling the touch sensations. Muscle weaknesses, loss of sensation in the legs and/or arms are the resultant symptoms may arise in the patient suffering from GBS. The symptoms will start in the legs and further spread to face and arms. In GBS 20–30% peoples may experience the chest muscle affected and difficulty in breathing. Sometimes the swallow and speak abilities also get affected. Most of peoples recover fully from GBS, but some people have long-term nerve damage. 3–5% of GBS patients may die from complications, which include paralysis of the muscles that control breathing, blood infection, lung clots or cardiac arrest. As per the National Health Portal web site information the cause of GBS is unknown. It sometimes linked with triggering by an infectious illness like gastrointestinal infection or a lung infection. Some countries from Europe and Asia have also reported familial occurrence of GBS. According to World Health Organization (WHO) overall incidence of GBS is 0.4 to 4.0 people per 100000 per year.[1]

**Keywords:** Autoimmune disease; Guillain-Barré syndrome (GBS); Systemic lupus erythematous; World health organization (WHO).

## Introduction

An autoimmune disease is a condition in which a person's immune system mistakenly attacks his/ her body organs. The immune system normally protects us from bacteria and viruses. Immune System on sensed bacteria and viruses as foreign invaders, it sends out an army of fighter cells to attack them. Immune system has capacity to identify which are foreign cells and which are own cells?

In case of an autoimmune disease, the immune system by mistakes recognizes our own body organs like your joints or skin, as foreign. Than it releases proteins called autoantibodies that attack healthy cells. Some common examples of autoimmune disease are Type 1 diabetes damages the pancreas,

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systemic lupus erythematous (SLE), affect the whole body, Guillain-Barré syndrome (GBS) in which peripheral nervous system affected.[2]

Guillain-Barré syndrome (GBS) is referred to a rare condition in which a person's self-immune system attacks his own peripheral nerves. The disease was first diagnosed by the French physician Jean-Baptiste Octave Landry in 1859. After this during 1916, Georges Guillain, Jean Alexandre Barré, and André Strohl also diagnosed two soldiers with the illness and described the albumin cytological dissociation of increased spinal fluid protein concentration but a normal cell count.

The disease can affect the people of all ages but more common in adults and in males. The disease has recovery if treated. In case of severity which is rare can lead to total paralysis. Guillain-Barré syndromecan adversely affect the nerves that control muscle movement, transmit pain, temperature, feeling the touch sensations. Muscle weaknesses, loss of sensation in the legs and/or arms are the resultant symptoms may arise in the patient suffering from GBS. The symptoms will start in the legs and further spread to face and arms. In GBS 20–30% peoples may experience the chest muscle affected and difficulty in breathing.

Sometimes the swallow and speak abilities also get affected. Most of peoples recover fully from GBS, but some people have long-term nerve damage. 3%-5% of GBS patients may die from complications, which include paralysis of the muscles that control breathing, blood infection, lung clots or cardiac arrest.

## Symptoms

Guillain-Barré syndrome started with symptom of weakness or tingling sensations starting from Legs. This can spread to arms and face. These symptoms can lead to paralysis of the legsarms, or muscles in the face for some peoples.

The ability to speak and swallow may become affected in severe cases of Guillain-Barré syndrome. These cases are considered life-threatening, and affected individuals should be treated in intensive-care units. Most people recover fully from even the most severe cases of Guillain-Barré syndrome, although some continue to experience weakness. About 3–5% of Guillain-Barré syndrome patients die from complications, which can include paralysis of the muscles that control breathing, blood infection, lung clots, or cardiac arrest.[1]

## Causes

Guillain-Barré syndrome caused after bacterial of viral infection. Guillain-Barré syndrome may also be triggered by vaccine administration or surgery. It is observe that there is increased number of cases of GBS in countries having Zika Virus infections high in numbers[1]. Guillain-Barré syndrome has at least four subtypes of acute peripheral neuropathy. The histological appearance of the acuteinflammatory demyelinating polyradiculoneuropathy (AIDP) subtype is similar to the experimental autoimmune neuritiscaused by T-cells directed against peptides from the myelin proteins P0, P2, and PMP22. The exact role of T-cell-mediated immunity in AIDP is not clear while there is evidence for the involvement of antibodies and complement. There is evidence that axonal subtype of Guillain-Barré syndrome, acute motor axonalneuropathy (AMAN), and acute motor and sensory axonal neuropathy (AMSAN), are initiated by antibodies togangliosides on the axolemma that target macrophages to invade the axon at the node of Ranvier. About a quarter ofpatients with Guillain-Barré syndrome have had a recent *Campylobacter jejuni* infection, and axonal forms of the diseaseare especially common in these people.[6]

## Classification of GBS

As per symptoms the GBS is classified into axonal and demyelinating forms.

*Sensory and motor:* AIDP or acute motor-sensory axonal neuropathy (AMSAN).

*Motor:* Acute motor demyelinating neuropathy (AMDN) or Acute motor axonal neuropathy (AMAN)

*Miller-Fisher syndrome:* Ophthalmoplegia, ataxia, and areflexia or also referred to as Fisher's syndrome. Bickerstaff's brainstem encephalitis (BBE): similar to Miller-Fisher syndrome but also has encephalopathy or hyper-reflexiaor both.[7]

*Pharyngeal-cervical-brachial:* Acute arm weakness, swallowing dysfunction, and facial weakness.[8]

*Acute pandysautonomia:* Diarrhoea, vomiting, dizziness, abdominal pain, ileus, orthostatic hypotensionand urinary retention, bilateral tonic pupils, fluctuating heart rate, decreased sweating, salivation, andlacrimation.[9,10] Pure sensory: acute sensory loss, sensory ataxia, and areflexia but no motor involvement.[11]

## Diagnosis

The diagnosis of Guillain-Barré syndrome itself is simple for the neurologist to diagnose. Diagnostic criteria exist and have stood the test of time. Many GBS patients show an acute neuropathy reaching a peak in duration of 4 weeks, weakness, hyporeflexia or areflexia, and indicated raised protein concentrations in CSF.[6] In patients lacking sensory involvement other disorders like poliomyelitis, myasthenia gravis, electrolyte disturbance, botulism, or acute myopathy also needed to be looked. Hypokalaemia is a often ignored alternative diagnosis. Once the diagnosis of an acute peripheral neuropathy is confirmed, Guillain-Barré syndrome indicated, but it will not be the only, cause. The Physician may also look for alternative causes such as diphtheria, vasculitis, porphyria, tick paralysis, and toxic neuropathy while examining the patient and taking their history.[6]

### *Indian Scenario on GBS Research*

Some case based studies were reported in India and as such there are no incidence studies of GBS was executed among Indians.[3,4] In the review article titled as India's contribution on "Guillain-Barre syndrome": Mapping of 40 years research by Shri Ram concluded that bibliometric analysis of literatures on GBS available through Scopus database during 1973–2012 revealed that research on GBS is running on in many countries specially USA has maximum numbers of literatures on GBS approximately 22.48% of global share. In context of India, it is on 10$^{th}$ number in overall publication. The Sanjay Gandhi Post-graduate Institute of Medical Research at Lucknow published maximum papers among Indian Organizations 31 publications. The Fig. 1 stated that the Axonal GBS in India has 8% patients of world.

## Conclusion

The Guillain-Barré syndrome (GBS) is disease which is not so common in India. If not treated, than it can lead to the death also. In its type the disease is unique in autoimmune diseases. The attack on Peripheral Nervous System and commonness in symptoms with other nervous disorder sometime confuse treating physician. The proper diagnosis is the key to manage Guillain-Barré syndrome (GBS). In Zika Virus affected countries there is greater risk of Guillain-Barré syndrome (GBS), hence these countries can take precautionary actions. These countries can train their doctors for the treatment and diagnosis of the disease.

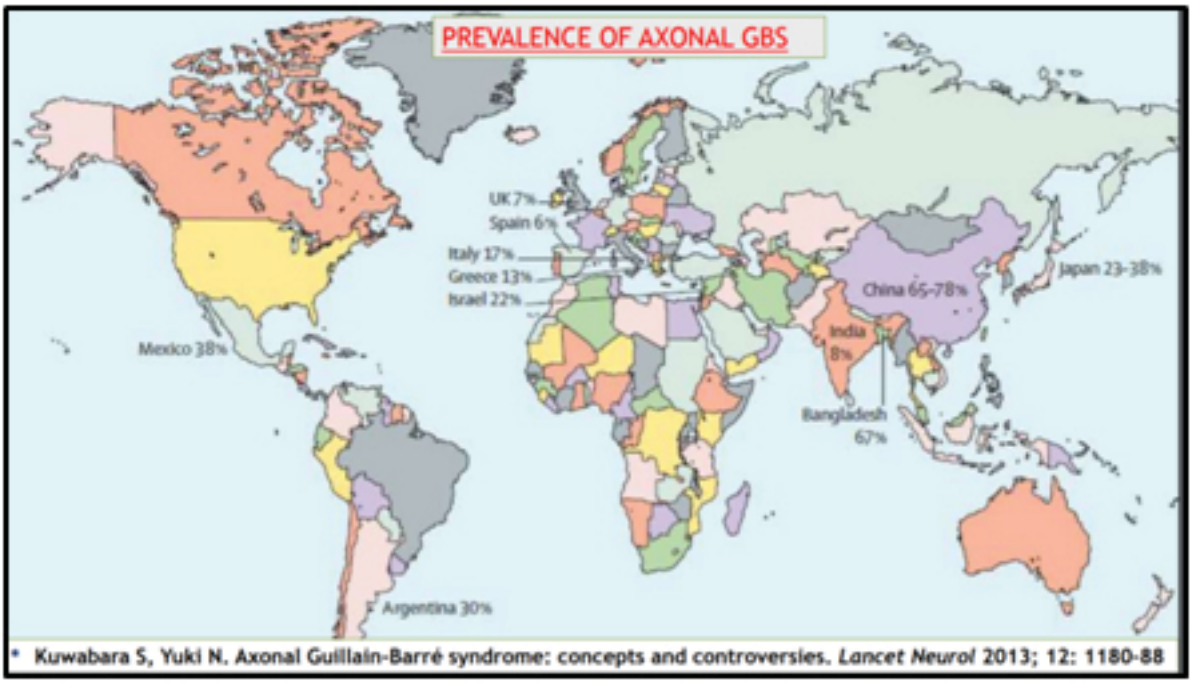


**Fig. 1:** Prevalence of axonal GBS Worldwide (2013).

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*Case Report*

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# A Symptomatic Case of Leptospirosis in Pregnancy

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**Abstract**

*Aim of the Study:* The aim of the study is to present a case of leptospirosis in pregnancy with uncommon presentation. *Introduction:* Leptospirosis is a zoonotic disease and has varied manifestation with overlapping features of malaria, hepatitis, typhoid and dengue. Leptospirosis is uncommon and difficult to diagnose due to its non-specific clinical presentation. *Case description:* A 26-year-old multigravida with 28 weeks of gestation, presented to the obstetrics outpatient department of our hospital with the chief complaints of high grade fever associated with chills, myalgia, nausea and vomiting. She also complained of having giddiness. She gave history of having oliguria and passage of dark colored urine. Following investigations were carried out: blood glucose, Liver function tests included serum total and direct bilirubin, AST, ALT, total protein and albumin, renal function tests included BUN and creatinine and C- reactive protein as inflammatory marker. Laboratory findings included high serum AST, ALT, total and direct Bilirubin, BUN, S. Creatinine, C- reactive protein and leukocytosis. Hemoglobin, S. total protein, albumin and random blood sugar were reported low. Urine analysis was positive for proteinuria. Peripheral smear was negative for malaria. Serological tests were negative for typhoid, hepatitisand dengue. Serological test was positive for antibodies (IgM) to leptospira at titer of 1:1,000. Diagnosis of leptospirosis was confirmed and management was carried out for the same. *Conclusion:* Since leptospirosis often presents with symptoms which overlap with the clinical features of malaria, dengue, hepatitis, enteric fever, therefore these conditions can be considered in the differential diagnosis of leptospirosis in pre exposure cases associated with pregnancy. *Clinical Significance:* Due to its nonspecific presentation, its diagnosis can be overlooked. It is important to have a high index of suspicion, for early diagnosis of the disease and start treatment, so as to avoid complications especially in pregnant women.

**Keywords:** Hyperbilirubinemia, leptospirosis, pregnancy, proteinuria.

## Introduction

Leptospirosis is a rare but an important infectious zoonotic disease caused by the bacteria spirochete of the genus, Leptospira. Infection in humans can occur either by direct contact with the urine or tissues of the infected animals especially rodents or indirectly through water, soil or vegetation, which is contaminated with the urine of the infected animal.[1] The bacteria can enter the body through damaged skin via cuts or abrasions, conjunctivae exposure andmucous membrane or via inhalation of microscopic droplets.[2]

The disease often presents with avaried manifestation with overlapping features of malaria, hepatitis, typhoid, dengue and others. It mimics other viral, bacterial and parasitic infections, acute fatty liver, pregnancy-induced hypertension, and

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HELLP syndrome. Due to its nonspecific clinical presentation its diagnosis is often tend to be overlooked.

We report a symptomatic case of leptospirosis in a pregnant woman herein, who presented in her third trimester of pregnancy and subsequently delivered a healthy baby.

## Case Report

A 26-year-old multigravida with 28 weeks of gestation, presented to the obstetrics outpatient department of our hospital with the chief complaints of high grade fever associated with chills, myalgia, nausea and vomiting. She also complained of having giddiness. She gave history of having oliguria and passage of dark colored urine. She was pale, lethargic, disoriented and icteric. On examination: she was found to be febrile with a temperature of 100°F, was hypotensive with blood pressure of 96/72 mmHg, and a high pulse rate of 122/min.

Blood sample was collected for biochemical profile, hemogram and serological investigations. Blood glucose, Serum AST, ALT, BUN were analysed by enzymatic colorimetric method, Total and direct bilirubin by diazo method, kinetic assay of creatinine was carried out by Jaffe's method, total protein by Biuret method, serum albumin by BCG dye binding method and C- reactive protein by immunoturbidimetric method. All biochemical parameters were assayed on Cobas 6000 and Hemogram assay on Sysmex XN-1000. Urine routine was done by multi strip dipstick. Leptospira IgM antibody was detected using ELISA method.

The investigation reports were as follows, RBS was 73 mg/dL, BUN was 22 mg/dL, S. creatinine was 2.2 mg/dL, Total bilirubin was 11 mg/dL, direct bilirubin was 8 mg/dL. AST was 146 U/L, S. ALT was 137 U/L, S. total protein was 6 g/dL, S. albumin was 2.8 g/dL, C- Reactive protein was 110 mg/L. Hemoglobin was 9 g/dl and leukocytosis was present. Urine analysis showed proteinuria (++). Peripheral smear was negative for malaria. Widal agglutination test was negative for typhoid. Serological tests were negative for hepatitis and dengue. Blood and urine culture was negative. Subsequently, serological test was positive for antibodies (IgM) to leptospira at a titre of 1: 1,000.

She had features of hypoglycaemia associated with jaundice, altered levels of serum liver enzymes and decreased renal function

So, the patient was diagnosed to have leptospirosis and was admitted in the hospital where she was treated with intravenous ceftriaxone and adequate hydration was given. She was intensively monitored and her condition started improving gradually. She was discharged and came back for follow up after a week. A couple of weeks later, she delivered a healthy baby, with no signs of congenital leptospirosis.

## Discussion

Leptospirosis in pregnancy has been reported sparsely in our country. Around 90% of the cases are mild and often present with non-specific symptoms. In the initial phase they present with features associated with fever, headache, chills, myalgia, abdominal pain, diarrhea, anorexia, vomiting. In the next phase present with lymphadenopathy, rash and hepatosplenomegaly associated with circulating IgM antibodies.[3] Whereas rest of the 5–10% of cases present with the more severe hemorrhagic form known asicteric leptospirosis/ Weil's disease, which includes involvement of vital organs such as liver, kidney and lungs, with a relatively high fatality rate 20–40%.[3]

Weil's disease is characterized by jaundice, pulmonary hemorrhage and renal dysfunction. Severe liver disease, i.e. Weil's disease has been linked with acute *leptospira* infection.[4–7] Leptospira infiltration of Disse space can detach the intercellular junctions, disruption of canaliculi causes leakage of bile predisposing to jaundice. Due to disruption of intercellular junction causes mild elevation of serum transaminases (AST/ALT). Due to increased protein catabolism with decreased protein synthesis due to liver inflammation associated with proteinuria can cause decrease in serum protein and albumin levels.[8,9] Diffuse tubulointerstitial inflammation can cause tubular necrosis and glomerular dysfunction can be due to infiltration with the inflammatory cells.[10] Myalgia in abdomen mimics as abdominal pain.

In this case, serum bilirubin is comparatively more elevated as compared to rise in liver enzymes. Hyperbilirubinemia can be either due to hepatocellular dysfunction, magnified by impairing bilirubin excretion from renal failure or from bilirubin over production from tissues haemorrhage.

Leptospirosis can also be transmitted through breast milk in case of neonatal leptospirosis.[3] Fetal implications of the disease in pregnancy

include healthy babies or can cause unforeseen outcomes including abortion, fetal death, still birth or congenital leptospirosis, depending upon the period of pregnancy.[11]

## Conclusion

Since the disease often presents with symptoms which overlap with the clinical features of malaria, dengue, hepatitis, enteric fever, therefore these conditions can be considered in the differential diagnosis of leptospirosis. In the third trimester of pregnancy, abdominal pain associated with jaundice, hemolysis, raised transaminases and coagulation abnormalities, include HELLP syndrome and AFLP (acute fatty liver of pregnancy) as the likely differentials.

### *Clinical significance*

Leptospirosis is an uncommon disease which often becomes difficult to diagnose due to its non-specific presentation. Therefore, it is important to have a high index of suspicion, in order to pick up the disease early and start treatment, so as to avoid complications specially in pregnant women.

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**Reference from electronic media**

[9] National Statistics Online—Trends in suicide by method in England and Wales, 1979-2001. www.statistics.gov.uk/downloads/theme_health/HSQ20.pdf (accessed Jan 24, 2005): 7-18. Only verified references against the original documents should be cited. Authors are responsible for the accuracy and completeness of their references and for correct text citation. The number of reference should be kept limited to 20 in case of major communications and 10 for short communications.

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