IntRoductIon
Bruns‑Garland syndrome (BGS) continues to be a contentious topic even 100 years after its discovery. Its lifelong incidence is 1% amongst diabetic individuals and affects middle aged‑elderly individuals with type 2 diabetes mellitus (usually not poorly controlled). Methods: The data presented in this review was collated from studies published on PubMed, MEDLINE and Google Scholar in October 2021. The search words included: “Bruns‑Garland syndrome,” “diabetic amyotrophy” and “diabetic lumbosacral radiculoplexus neuropathy” and “proximal diabetic neuropathy.” Results: The exact pathophysiology is debatable but an ischemic pathology (non‑systemic microvasculitis) is most plausible. Its cardinal symptoms include acute onset of severe proximal lower extremity pain followed by weakness and wasting, some sensory loss, weight loss and autonomic symptoms. Conclusion: The prognosis is good as most patients improve to near‑normal strength with pain cessation within 18 months of onset.

Abstract
Background and Aims: Bruns‑Garland syndrome (BGS) continues to be a contentious topic even 100 years after its initial discovery. It was originally described by Bruns[1] in 1890 and later by Garland and Taverner in a case series in 1955.[2‑5] They described this syndrome as one characterized by asymmetric, lower extremity‑predominant symptom complex occurring in patients with short and “nonsevere” diabetes and coined the often used but erroneous term “diabetic amyotrophy.” The term amyotrophy makes one refer the localization to muscle or anterior horn cell. For this reason, multiple other nomenclature have been described for it: Proximal diabetic neuropathy,[6‑8] diabetic proximal amyotrophy,[9] diabetic lumbosacral plexopathy,[10,11] femoral‑sciatic neuropathy[12] and femoral neuropathy,[13,14] and diabetic lumbosacral radioculo‑plexo‑neuropathy.[15] There is some correctness in all of these, but we support the eponym Bruns‑Garland syndrome. This not only prevents future confusion, but also follows the working precedent established for diseases like Guillain‑Barré syndrome and Emery‑Dreifuss muscular dystrophy, where descriptive terms are misleading.[16]

The lifelong incidence of BGS is approximately 1% among diabetic individuals[17] and generally affects middle‑aged elderly individuals with type 2 diabetes mellitus. The diabetes mellitus is usually not poorly controlled may occur soon after diagnosis or may be the presenting feature leading to its diagnosis.[16]

Materials and Methods
The data presented in this review were collated from studies published on PubMed, MEDLINE, and Google Scholar in October 2021. The search was conducted by AA and VVY and the search words included the following: “Bruns‑Garland syndrome,” “diabetic amyotrophy” and “diabetic lumbosacral radiculoplexus neuropathy,” and “proximal diabetic neuropathy.” These articles were thereafter screened for relevance and all articles with human patients and published in English till December 2021 were included. Only one unpublished randomized controlled trial (RCT; abstract published) by Dyck et al.[18] was found, with the remainder being case series or reports.

Etiopathogenesis, clinical presentation, and evaluation
The exact pathophysiology of BGS is debatable but a painful onset and subacute, progressive course suggest an ischemic pathology in the form of a nonsystemic microvasculitis. Many studies conducted biopsies on the sural and intermediate cutaneous nerve of thigh and showed features supportive of this hypothesis.[19‑21] Inflammatory changes were found involving the epineural vessels, including vasculitis or inflammatory infiltrates. Immunostaining

Address for correspondence: Dr. Venugopalan Y. Vishnu, Department of Neurology, Room No 704, Cardioneurosciences Centre, AIIMS, New Delhi, India. E‑mail: vishnuvy16@yahoo.com

Submitted: 09‑Mar‑2022 Revised: 29‑Apr‑2022 Accepted: 30‑Apr‑2022
Published: 14‑Jul‑2022

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution‑NonCommercial‑ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non‑commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

DOI: 10.4103/aiian.aiian_239_22
also revealed increased nuclear factor-κB staining and ICAM-1 cells in the blood vessels supporting a dysimmune vascular pathogenesis.[22]

The usual age of presentation of BGS is the sixth decade of life (median onset: 60 years) with a slight male predilection (male: female-3:2). It occurs within a few years of diagnosis of diabetes mellitus (median: 3 years).[15] Occasionally, its presence sometimes led to the diabetes diagnosis and is commoner with type 2 diabetes. The blood sugar control is usually good with no concomitant microvascular complications (nephropathy and retinopathy) are present. However, some patients can present with poor glycemetic control. There was no correlation with the use of any particular hypoglycemic agent (oral drugs vs insulin).

Its cardinal symptoms included acute onset of severe proximal lower extremity pain followed by weakness, mild-to-moderate sensory loss, weight loss, and autonomic symptoms.[15] Pain involves the thigh, hip, or back and is unilateral in most cases (approximately 70%) and is asymmetric in bilateral cases. It is severe in intensity and deep aching in character (with or without paresthesia). This is succeeded in a few weeks by atrophy and weakness of the afflicted muscles (predominantly: quadriceps, hip adductors, and iliopsoas).[23] which is again proximal predominant. It is unilateral in 25% cases and bilateral but asymmetric in the remaining cases. This contralateral spread occurs within 6 months. A small proportion developed can progress to develop diffuse weakness leading to quadriaparesis or cause upper limb involvement as well. Progression in the involved limb to cause distal weakness occurs in 60% of cases.[15] The afflicted region has loss of reflexes. Distal symmetric sensory involvement is also common, but not clinically useful because of its nonlocalizing value. Approximately, a quarter of cases have associated autonomic dysfunction. Significant weight loss is a common accompaniment, and usually begins with symptom onset. Rarely, symptom onset suggestive of cervical radiculoplexus neuropathy may occur.[24] These patients have similar findings as mentioned above but in the upper limbs. Table 1 lists the differences between the 2 presentations.

Examination characteristically reveals weakness in the proximal muscles of the affected limb with concomitant atrophy of hip adductors, quadriceps, and iliopsoas. Mild distal sensory loss may be present due to coexistent diabetic distal symmetrical polyneuropathy (DSPN). The knee jerks are absent and the ankle jerks are usually preserved. However, the latter can be lost with underlying DSPN.[23]

Nonetheless, the eventual prognosis is good as most patients tend to improve to near-normal strength with pain cessation within 18 months of symptom onset. Some distal weakness may persist in 50% cases and around 10% to 15% can develop relapsing symptoms.

However, approximately 10% patients might continue to be dependent for ambulation with incomplete recovery after 2 years of onset.[15]

| Table 1: Comparison between diabetic lumbosacral and cervical radiculoplexus neuropathies |
|---------------------------------|---------------------------------|---------------------------------|
|                                | Diabetic lumbosacral radiculoplexus neuropathy | Diabetic cervical radiculoplexus neuropathy |
| Male:female                    | 3:2                                      | 2:1                                      |
| Median age at onset (in years) | 60                                       | 62                                       |
| Most common presenting symptom | Pain                                      | Pain                                      |
| Progression                    | No pain-10%                              | No pain-20%                              |
|                               | Chronic for 12-18 months in the majority | Chronic progression (>1 month) in 15% cases |
| Bilateral involvement         | 85%                                      | 47%                                      |
| Weight loss                    | >50%                                     | 35%                                      |
| CSF protein elevation         | 85%                                      | 90%                                      |
| NCS/EMG                        | Sciatic/femoral/obturator nerve and lumbar roots | Upper plexus-52% Middle plexus-45% |

Since the diagnosis is mainly clinical, a few similarly presenting differential diagnoses need to be excluded. Neoplastic lumbosacralplexopathy needs to be always excluded and the role of neuroimaging in BGS is predominantly for this purpose. If present, it reveals infiltration of lumbosacral nerve roots by the tumor leading to this presentation.

Cauda equina syndrome and spinal canal stenosis can rarely present in this fashion and can also be diagnosed by neuroimaging. GBS and chronic inflammatory demyelinating polyneuropathy can also mimic BGS but clinical clues like progression for <1 month, nerve thickening, and demyelinating pattern on nerve conduction studies (NCS) help clinch the diagnosis.[23,24]

Diagnostic evaluation for BGS is supportive and no gold standard test is available at present. The diagnosis is made on the basis of a thorough history and examination. Magnetic resonance imaging of the lumbosacral spine is usually performed to rule out structural causes that can manifest similarly. Magnetic resonance imaging findings in BGS include lumbosacral enhancement in the roots, plexus, and nerves with T2 hyperintensities in the involved muscles.[25] The cross- sectional area of these structures is also increased compared with controls.[26] However, these changes are nonspecific and can be seen in inflammatory radiculoneuropathies and radiculitis. Hlis et al.[27] showed that neuromuscular lesions secondary to BGS can be qualitatively and quantitatively identified by magnetic resonance neurography and diffusion tensor imaging, and that the most commonly affected structures were the femoral and sciatic nerves followed by lumbosacral nerve roots and finally obturator nerves. They also revealed a positive correlation of apparent diffusion coefficient values with the patient’s hemoglobin A1c levels.
Therefore, these tests can be employed when BGS is suspected. NCS reveal an amplitude drop of the nerves of the affected region suggestive of axonal neuropathy and electromyography (EMG) findings are those of the involved muscles showing active denervation with or without reinnervation suggestive of a lumbosacral plexopathy. However, paraspinal involvement is common, which is indicative of concomitant radicular involvement, and should always be tested. These EMG findings are commonly asymmetric, with more severe affliction of one side. A normal NCS and EMG study in a suspected BGS patient is a red flag and should prompt a diagnostic reconsideration.

Cerebrospinal fluid analysis may sometimes be done classically, which reveals elevated protein (median: 90 mg/dL) and normal cells (albumin-cytological dissociation) in approximately 85% patients. This finding is similar to that found in GBS or chronic inflammatory demyelinating polyneuropathy and does not add to diagnosis and is not routinely advocated for diagnostic evaluation for this reason. The presence of pleocytosis is a red flag and should prompt a search for mimics.

Testing for other autoimmune diseases is unlikely to add to the diagnostic yield. Inflammatory markers like erythrocyte sedimentation rate and C-reactive protein tend to be raised in 20% cases but are nonspecific. Glycosylated hemoglobin A1c values tend to be mildly elevated with median value of 8.0%. Nerve biopsies are not recommended. Nerve biopsy studies done till date were done either on the intermediate cutaneous nerve of the thigh or the sural nerve. Those done on the latter are of unclear relevance, because the sural nerve contains axons derived from the S1 nerve root, whereas clinical findings predominantly localize to the axons from the L2-L4 nerve roots.[28]

The treatment of BGS focusses on pain control and improvement in strength above and beyond good euglycemic control. Pain is treated with drugs that have been proven to be effective in managing painful DSPN like selective serotonin reuptake inhibitors, tricyclic antidepressants, anticonvulsants, and selective noradrenaline reuptake inhibitors.[15,23]

Some improvement in pain is also seen with immunotherapy agents. The prototypical treatment protocol for motor improvement remains controversial in the absence of evidence from RCTs. Due to a postulated microvasculitic etiology, treatment with immunotherapy seems prudent apart from basic supportive measures. The latter includes active physiotherapy and usage of assistive devices to enhance motility. Despite widespread interest in immunotherapy, results from various studies have been inconsistent and conflicting.[29] Corticosteroids are often used as a first-line agent. Dyck et al.[18] showed improvement in neuropathic pain and secondary endpoints but no significant improvement in motor power with intravenous methylprednisolone. Kendal et al.[30] showed some improvement in strength with intravenous immunoglobulin. Most of these patients, however, also received intravenous or oral steroids. Pascoe et al.[31] showed improvement in 4 out of 5 patients treated with plasma exchange with or without intravenous immunoglobulin. Similar findings were also exhibited by Jaradeh et al.[32] in 9 patients. However, considering all these studies were not RCTs and a natural tendency toward improvement after 12 to 18 months, these results need to be interpreted with caution. Patients can be depressed considering the background of acute/subacute onset painful weakness and may need reassurance and antidepressants.

**Conclusion**

BGS is a rare diabetic complication but considering the humongous number of patients living with diabetes, it is likely to encounter frequently. This warrants increasing awareness about it and its management among neurologists and nonneurologists (endocrinologists and primary physicians). Immunotherapy is controversial and their use should be weighed based on pros and cons of treatment. Earlier recognition will lead to rapid diagnosis, which might provide new insights into pathophysiology and progression, and an RCT is needed to answer the perpetual query whether to treat or not to treat with immunotherapy.

**Research highlights**

1. Cardinal symptoms of BGS are acute onset of severe proximal lower extremity pain followed by weakness and wasting
2. Exact pathophysiology is debatable but nonsystemic microvasculitis is most plausible
3. Usually self-limiting with pain cessation and near normal power attainment within 18 months of onset
4. Immunotherapy is controversial.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Brunns L. Ueber neuritische Lähmungen beim diabetes mellitus diabetes mellitus. Berl Klin Wochenschr 1890;27:509‑15.
2. Garland H, Taverne D. Diabetic myelopathy. Br Med J 1953;1:1405‑8.
3. Garland H. Diabetic amyotrophy. Br Med J 1955;2:1287‑90.
4. Garland H. Diabetic amyotrophy. Br J Clin Pract 1961;15:9‑13.
5. Garland H. Neurological complications of diabetes mellitus: Clinical aspects. Proc R Soc Med 1960;52:137‑14.
6. Williams IR, Mayer RF. Subacute proximal diabetic neuropathy. Neurology 1976;26:108‑16.
7. Ashbury AK. Proximal diabetic neuropathy. Ann Neurol 1977;2:179‑80.
8. Subramony SH, Wilbourn AJ. Diabetic proximal neuropathy: Clinical and electromyographical studies. J Neurol Neurosci 1982;53:293‑304.
9. Chokroverty S. Proximal nerve dysfunction in diabetic proximal amyotrophy. Electrophysiology and electron microscopy. Arch Neurol 1982;39:403‑7.
10. Bastron JA, Thomas JE. Diabetic polyradiculopathy: Clinical and electromyographic findings in 105 patients. Mayo Clin Proc 1981;56:725‑32.
11. Bradley WG, Chad D, Vergheese JP, Liu HC, Good P, Gabbai AA, et al. Painful lumbosacral plexopathy with elevated erythrocyte sedimentation
rate: A treatable inflammatory syndrome. Ann Neurol 1984;15:457-64.
12. Gydell K, Skanse B. A rare type of femoral-sciatic neuropathy in diabetes mellitus. Acta Med Scand 1956;155:463-8.
13. Goodman JI. Femoral neuropathy in relation to diabetes mellitus: A report of 17 cases. Diabetes 1954;3:266-73.
14. Calverley JR, Mulder DW. Femoral neuropathy. Neurology 1960;10:963-7.
15. Albers JW, Jacobson RD, Smyth DL. Diabetic amyotrophy: From the basics to the bedside. EMJ 2020;5:94-103.
16. Barohn RJ, Sahenk Z, Warmolts JR, Mendell JR. The Bruns-Garland syndrome (diabetic amyotrophy) revisited 100 years later. Arch Neurol 1991;48:1130-5.
17. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: The Rochester diabetic neuropathy study. Neurology 1993;43:817-24.
18. Dyck PJB, O’Brien P, Bosch EP, Grant I, Burns T, Windebank A, et al. The multi-centre double blind controlled trial of IV methylprednisolone in diabetic lumbosacral radiculoplexus neuropathy. Neurology 2006;66 (5 Suppl 2):A191.
19. Said G, Goulet-Coteau C, LaCroix C, Moulonguet A. Nerve biopsy findings in different patterns of proximal diabetic neuropathy. Ann Neurol 1994;35:559-69.
20. Llewelyn JG, Thomas PK, King RH. Epineurial microvasculitis in proximal diabetic neuropathy. J Neurol 1998;245:159-65.
21. Younger DS. Diabetic lumbosacral radiculoplexus neuropathy: A postmortem studied patient and review of literature. J Neurol 2011;258:1364-7.
22. Kawamura N, Dyck PJB, Schmeichel AM, Engelstad JK, Low PA, Dyck PJ. Inflammatory mediators in diabetic and non-diabetic lumbosacral radiculoplexus neuropathy. Acta Neuropathol 2008;115:231-9.
23. Nagsay S, Somashekhar C, James CM. Diagnosis and management of diabetic amyotrophy. Endocrinology 2010;327-9.
24. Collins MP, Hadden RD. The nonsystemic vasculitic neuropathies. Nat Rev Neurol 2017;13:302-16.
25. Filosto M, Puri E, Cotelli M, Todeschini A, Vielmi V, Rinaldi F, et al. MR neurography in diagnosing nondiabetic lumbosacral radiculoplexus neuropathy. J Neuroimaging 2013;23:543-4.
26. His R, Poh F, Bryant M, Xi Y, Chhabra A. Quantitative assessment of diabetic amyotrophy using magnetic resonance neurography—a case-control analysis. Eur Radiol 2019;29:5910-9.
27. Hlis R, Poh F, Xi Y, Chhabra A. Diffusion tensor imaging of diabetic amyotrophy. Skeletal Radiol 2019;48:1705-13.
28. Wilbourn AJ. Diabetic amyotrophy and its nondiabetic counterpart. Summary and Comment. Neurology 2002.
29. Chan YC, Lo YL, Chan ES. Immunotherapy for diabetic amyotrophy. Cochrane Database Syst Rev 2017;7:CD006521
30. Krendal DA, Costigan DA, Hopkins LC. Successful treatment of neuropathies in patients with diabetes mellitus. Arch Neurol 1995;52:1053-61.
31. Pascoe MK, Low PA, Windebank AJ, Litchy WJ. Subacute diabetic proximal neuropathy. Mayo Clin Proc 1997;72:1123-32.
32. Jaradeh SS, Prieto TE, Lobeck LI. Progressive polyradiculoneuropathy in diabetes: Correlation of variables and clinical outcome after immunotherapy. J Neurol Neurosurg Psychiatry 1999;67:607-12.