Cardiac autonomic neuropathy: impact on severe hypoglycemic unawareness and orthostatic hypotension in diabetic dysautonomia, a case series and review

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Diabetic autonomic neuropathy (DAN) and its associated cardiovascular autonomic neuropathy (CAN) can lead to potentially fatal complications. We analyzed two distinct cases of DAN/CAN based on comprehensive cardiovascular autonomic reflex tests (CARTs). Case 1 involves a 27-year-old patient with T1DM suffering from recurrent severe hypoglycemic unawareness due to DAN. After implementing an automated insulin delivery system, the glucose management improved significantly. Case 2 describes a 60-year-old patient with type 2 diabetes experiencing debilitating orthostatic hypotension. The initiation of Midodrine and Fludrocortisone markedly improved symptoms and capacity of daily activities. This observational study highlights the critical yet frequently overlooked severe manifestations of DAN/CAN, specifically hypoglycemic unawareness and orthostatic hypotension. CARTs play a pivotal role in confirming the diagnosis and guiding therapeutic decisions. Tailored interventions, including advanced technologies like automated insulin delivery systems for T1DM and pharmacotherapy targeting neurogenic orthostasis, can significantly improve patient outcomes and quality of life. *Cardiovasc Endocrinol Metab* 13: 1–6 Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Diabetic dysautonomia, also called diabetic autonomic neuropathy (DAN), is a serious yet underestimated complication. DAN can be manifested soon after diagnosis of type 1 diabetes (T1D) or type 2 diabetes (T2D) and is associated with an elevated standardized mortality rate [1]. The autonomic system (ANS) contains five components including parasympathetic cholinergic, enteric, sympathetic cholinergic, sympathetic adrenomedullary hormonal, and sympathetic noradrenergic. DAN impairs one or multiple components of the ANS leading to multisystem manifestations. One primary manifestation is cardiovascular autonomic neuropathy (CAN), defined as 'impairment of cardiovascular autonomic control in patients with established diabetes after excluding other causes' [2]. CAN includes a wide spectrum of disorders such as orthostatic hypotension (OH), abnormal circadian BP pattern, prolonged corrected QT (QTc) interval, and silent myocardial ischemia. The prevalence of CAN was 60% in T1D 15 years after the diagnosis and up to 91% in long-standing poorly controlled patients [3]. In T2D patients, it ranges from 31 to 73% depending on demographics and clinical status [4]. Neurogenic orthostatic hypotension (nOH) is a distinctive sign of CAN, which debilitates the patient by interfering with simple daily activities in fear of falling [5]. CAN also causes life-threatening complications such as arrhythmia and sudden cardiac death (SCD) independent of its well-established increased risk for ischemic cardiovascular disease and microangiopathic comorbidities [6]. Notably, CAN has a mortality rate of 16–50% over 5 years [7].

Besides CAN, DAN-related impaired glucose regulation has been overlooked. It causes recurrent severe hypoglycemic events (SHEs) with hypoglycemia unawareness (HU) [8]. According to the American Diabetes Association (ADA), level 1 hypoglycemia means a glucose level <70 mg/dl (3.9 mmol/L), which triggers the counter-regulatory response to hypoglycemia. Level 2 is the level <54 mg/dl (3.0 mmol/L), a situation associated with cognitive dysfunction and developing HU. Rather than a specific measurable value, SHEs (level 3) are defined as altered mental and/or psychical status necessitating assistance from another person to recover. HU, also called

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impaired awareness of hypoglycemia (IAH), is defined as a failure to sense the drop in blood glucose below normal levels or an occurrence of neuroglycopenia symptoms without sympathetic autonomic warning. A recent cross-sectional study investigated 2000 T1D patients and revealed a 20% prevalence of SHEs and 30% of IAH, with a high proportion of patients not achieving glycemic targets [9]. T2D patients had about 10% of IAH who were receiving insulin treatment compared with 23% who underwent hemodialysis [10]. Further evidence shows that SHEs and IAH have reciprocal effects as recurrent SHEs lead to IAH while IAH causes six-fold increased risk of SHEs [11]. Although antidiabetic medications and insulin cause SHEs, DAN has been suggested as the major mechanism underlying the SHEs/IAH cycle. SHEs/IAH cause falls, loss of consciousness, coma, seizures, cardiovascular events, and even death [12].

The consequences of DAN can be serious. However, DAN has always been overlooked. We presented two cases to underscore the critical need for early recognition and proactive management to mitigate the potentially fatal complications of DAN.

Case 1

A 27-year-old man with a history of T1D, diabetic gastroparesis, retinopathy, neuropathy, nephropathy, and anhidrosis presented with generalized weakness and vague abdominal pain for 2 weeks. He was using a continuous insulin pump at home, which was recently switched to manual insulin injection due to insurance authorization. He ate frequent small meals due to gastroparesis. Although only receiving Lispro 4–6 units before meals or no insulin if glucose was below 200 mg/dl (11.1 mmol/L), he experienced frequent SHEs at home. His other medications include lisinopril 10 mg once daily and garbapentin 300 mg three times daily.

On arrival, he had a BP of 194/105 mmHg, HR of 134 beats/min, and RR of 20 breaths/min with normal oxygen saturation. He was fully alert and oriented yet malnourished and fatigued. He had decreased vibration sensation in both feet with absent Achilles tendon reflex. Laboratory tests revealed a blood glucose of 440 mg/dl (24.4 mmol/L), creatinine 2.3 mg/dl, hemoglobin A1c (HbA1c) 12.1% g/dl with normal anion gap and bicarbonate, negative ketones and troponin, and undetectable c-peptide levels. No obvious abnormalities were observed in the urine analysis, coagulation tests, or other parameters (Supplementary Table 1, Supplemental Digital Content 1, *http://links.lww.com/CAEN/A64*). He met with the criteria for systemic inflammatory response syndrome and sepsis workup was started. A computed tomography scan of chest was unremarkable but abdomen and pelvis showed retention of stool and urine. He received intravenous fluids, Labetalol injection for hypertension and eight units of Lispro subcutaneously for hyperglycemia, soap enema with bowel regimens for constipation, and straight catheterization for urine retention.

Two hours later, he turned to be drowsy with glucose of 47 mg/dl (2.6 mmol/L) but no neurogenic hypoglycemia symptoms, such as pallor, sweating, nervousness or irritability, shaking or tremulousness. The hypoglycemia was immediately corrected by injecting 25 g of dextrose. At 2100 that day, glucose was 225 mg/dl (12.5 mmol/L), and he received four units of Glargine Insulin. At midnight, his glucose fell to 75 mg/dl, and he had juice and little food. At 0600 the next day, the patient was found to be lethargic in the bed with a Glasgow Coma Scale of 11 and glucose of 24 mg/dl (1.3 mmol/L), but otherwise normal BP, HR, and oxygen saturation without focal neurological deficit. After receiving 25 g of dextrose, he recovered to baseline. He suffered persistent nausea and bloating after eating food due to gastroparesis. He was managed with 2–4 units of Lispro every 6 h without long-acting insulin targeting a safer range of 300–420 mg/dl (16.7–23.3 mmol/L) and had no more SHEs/IAH episodes. The key clinical events and findings during hospitalization were listed in Fig. 1.

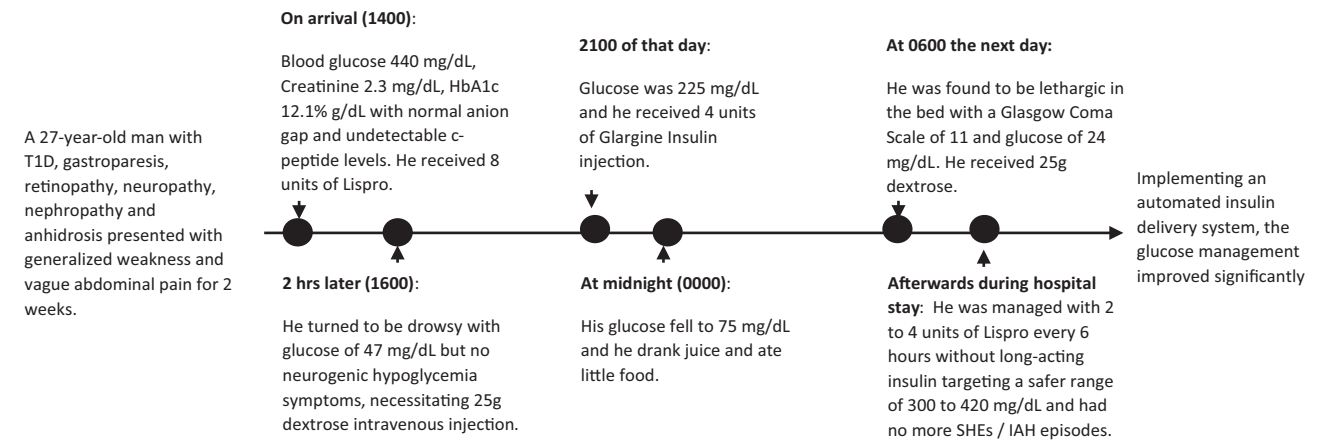
He received cardiovascular autonomic reflex tests (CARTs) and was diagnosed with CAN (Table 1). While still waiting for insurance authorization, he decided to relocate to his original state to resume the insulin pumping. After implementing an automated insulin delivery system, the glucose management improved significantly.

Case 2

A 60-year-old male with a long history of T2D, hypertension, paroxysmal atrial fibrillation, and heart failure with preserved ejection fraction presented with worsening postural lightheadedness for one week. He reported progressively worsening lightheadedness that he could barely stand up. Over the past few days, he was literally bed-bound to avoid falls. He had no chest pain, shortness of breath, headache, or vision changes. He was a nonsmoker, nondrinker, and had no illicit drugs. His medications included Apixaban 5 mg twice daily, Losartan 50 mg once daily, insulin Glargine 42 units daily, and Lispro 10 units before each meal in the past 2 years. He had multiple emergency visits over the past 6 months due to lightheadedness and recurrent falls. He was diagnosed with OH after a positive tilt table test 2 months ago. Losartan was discontinued and he started Midodrine 10 mg three times daily. Apixaban was discontinued to avoid intracranial hemorrhage due to frequent falls.

On arrival, orthostatic vital signs showed lying down: BP: 124/74 mmHg and HR: 93 beats/min; sitting up BP: 108/75 and HR: 92, and standing up BP: 64/37 and HR: 95. While standing up, he was significantly symptomatic with lightheadedness but otherwise no chest pain, palpitations, shortness of breath, or diaphoresis. No other abnormalities were found. The chemistry panel was nonsignificant

Fig. 1



Key clinical events and findings. IAH, impaired awareness of hypoglycemia; SHEs, severe hypoglycemic events; T1D, type 1 diabetes mellitus.

Table 1 **Cardiovascular autonomic reflex tests reports**

Tests	Techniques of test	Ranges of normal response	Results	
			Case 1	Case 2
Parasympathetic				
HR response to breathing	With resting and supine, monitoring HR by ECG while the patient breaths in and out at 6 breaths/min	A difference in HR of >15 bpm is normal, but <10 bpm is abnormal. The lowest normal value of the expiration-inspiration ratio of the R–R interval is 1.17.	Abnormal	Abnormal
HR response to standing	With ECG monitoring, measuring the R–R interval at beats 15 and 30 after standing	A tachycardia is followed by reflex bradycardia. The 30 : 15 ratio of R–R interval should be >1.03.	Abnormal	Abnormal
HR response to Valsalva	With ECG monitoring, forcibly exhaling a manometer to 40 mmHg for 15 s	There should be tachycardia during strain, followed by bradycardia with release. The normal ratio of longest to shortest R–R is >1.2.	Abnormal	Abnormal
Spectral analysis of HRV, high-frequency power	Commercially available computer programs	-		-
Sympathetic				
Spectral analysis of HRV, very low-frequency power	Commercially available computer programs	-	-	-
SBP to standing	Measuring SBP during supine and 2 min after standing	Normal is <10 mmHg; borderline is 10–29 mmHg; abnormal is >30 mmHg with symptoms	Abnormal	Abnormal
DBP to isometric hand grip	Squeezing a handgrip dynamometer to establish a maximum. Grip is to squeeze at 30% maximum for 5 min	Normal is to rise of DBP > 16 mmHg in the opposite arm	Abnormal	Abnormal

HRV can be assessed either by spectral analysis (frequency-domain analysis) of an array. In this spectral analysis, sympathetic/parasympathetic balance = VLFP/HFP. We did not assess spectral analysis in these cases. Clinical cardiac autonomic neuropathy is further classified into three groups: early involvement (one abnormality or two borderline results), definite involvement (≥2 abnormalities), and severe involvement (presence of orthostasis).
HFP, high-frequency power; HR, heart rate; HRV, heart rate variability; VLFP, very low-frequency power.

(Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/CAEN/A64*). Brain MRI and carotid artery duplex were unremarkable. An echocardiogram showed mildly impaired diastolic heart function. He received CARTs and was diagnosed with CAN and neurogenic OH (nOH) (Table 1). He received education on nonpharmacological approaches to minimize the postural symptoms and was prescribed fludrocortisone 100 mg once daily. At 1-month follow-up, he stated improved symptoms of postural lightheadedness with better daily functions. Orthostatic vital signs improved from a BP of 105/75 mmHg sitting to 92/65 mmHg standing up.

Discussion

Our first case had long-standing poorly controlled diabetes and DAN manifesting with profound parasympathetic impairments such as gastroparesis, constipation, and urine retention, symptomatic cholinergic failure as anhidrosis, and CAN. He suffered from recurrent dangerous SHEs/IAH making him poorly tolerant to manual insulin injection and thereby a big barrier to achieving recommended glycemic targets. This was in agreement with other studies as unpredictable variability in prandial glucose excursions due to gastroparesis leads to acute and chronic hyperglycemia accompanied by higher risk of

hypoglycemia, which forms a reciprocal downward spiral between hyperglycemia and gastroparesis [13].

Actually, DAN is involved in SHEs/IAH besides gastroparesis. First, DAN attenuates the activation of sympathoadrenal epinephrine with impaired autonomic sympathetic response to hypoglycemia [14,15]. Then, DAN causes impaired glucagon hormone response with glucagon deficiency. In addition, DAN lowers the glycemic threshold for symptomatic, autonomic, and cognitive dysfunction, which leads to reduced detection of hypoglycemia [16,17]. Furthermore, antecedent SHEs lead to hypoglycemia-associated autonomic failure (HAAF), a situation of acquired, reversible functional disorder in responding to hypoglycemia due to prior SHEs, which blunts the sympathoadrenal and autonomic activities with alterations in hypothalamic functions [18,19]. Evidence shows that HAAF can usually be reversed within 2–3 weeks of scrupulous avoidance of hypoglycemia [17], whereas DAN-induced SHEs/IAH is nonreversible due to small nerve fiber loss. Correspondingly, SHEs/IAH and HAAF compose a vicious cycle that perpetuates itself and leads to exacerbated neuroglycopenic symptoms of hypoglycemia, impeding glycemic control and leading to severe SHEs-related events like coma and death (Fig. 2).

DAN-induced SHEs/IAH have been suggested as a primary mechanism for dead-in-bed syndrome, meaning sudden death in people with T1D on insulin therapy. It facilitates prolonged QTc interval and fatal arrhythmia, which is different from SCD caused by diabetes-related coronary artery disease or chronic heart failure. Clinically, the Clark/Gold questionnaires are commonly used to assess IAH [20] and help to decrease SHEs/IAH, but provide limited benefits to DAN improvement.

This patient failed a traditional insulin pump evidenced by HbA1c of 12% and multiple other comorbidities. Actually, the traditional pump was formulated as a continuous basal infusion plus programmed bolus having limited benefits in patients with gastroparesis due to delayed unpredictable postprandial hyperglycemia. Advances in bioengineering and technology have enabled more precise matching of the insulin requirements to glucose excursions, such as the closed-loop insulin delivery system combines continuous glucose monitoring (CGM) with automated insulin delivery and minimal risk of SHEs/IAH [21,22]. Particularly, the real time- CGM device generates instantaneous glucose readings with alarms for extreme glucose levels and predictive alerts, mimicking a mechanical " hypo-/hyperglycemia awareness'' [23]. Accordingly, our patients benefit from this system.

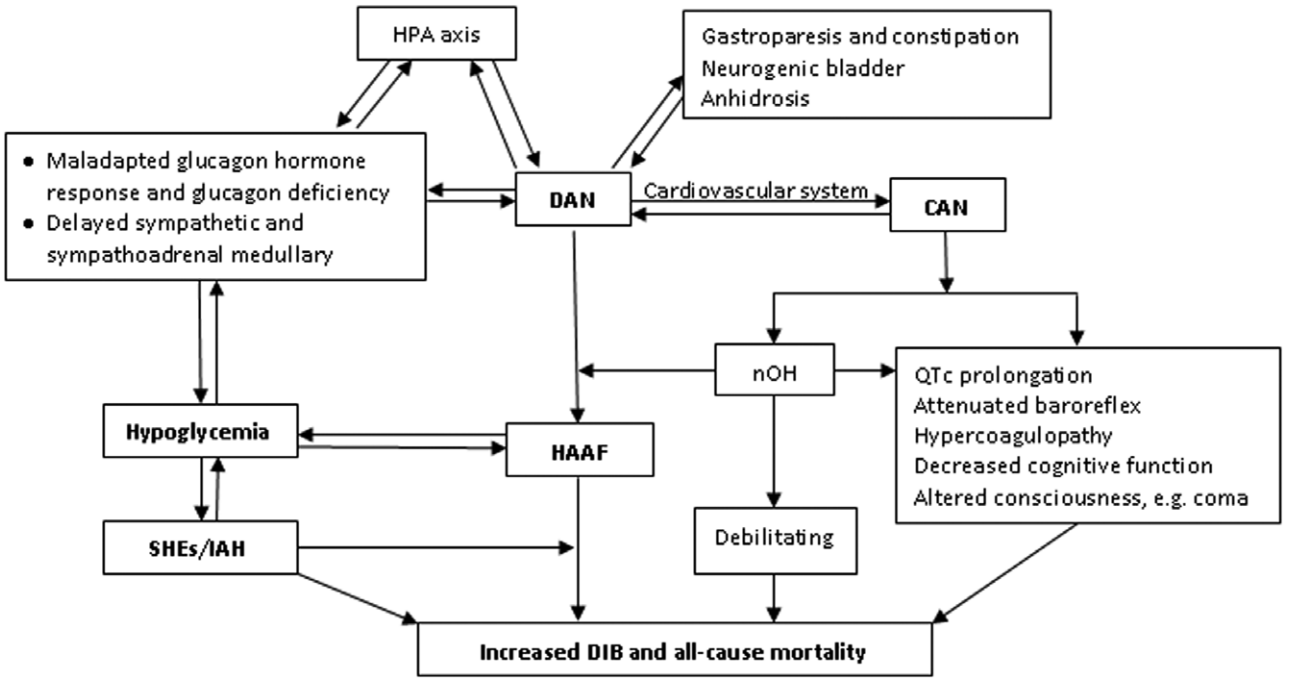
CAN is another crucial component of DAN linked to increased morbidity and mortality. Both patients met the criteria for CAN based on CARTs. As the gold standard test, CARTs are a battery of autonomic tests that measure the variability in HR and BP with various maneuvers which reflect sympathetic and parasympathetic functions (Table 1). Calculating heart rate variability from 5 min resting electrocardiography recordings increases the sensitivity of CARTs to 75% and specificity to 85% [24]. Clinical diagnosis of CAN is made when predominant changes present on CARTs, such as resting tachycardia and exercise intolerance or OH. Additionally, obtaining a score from CARTs can monitor the severity and progression of CAN [24]. It is recommended by ADA to screen for CAN upon diagnosing T2D and within 5 years of diagnosing T1D, particularly in the individuals with poorly controlled, unstable glycemia and multiple risk factors [25].

Our second patient developed neurogenic OH. As a subtype of OH, nOH can be differentiated by two methods. Firstly, nOH does not have orthostatic HR rise in spite of BP falls due to impaired baroreflex stimulation [6], while cardiac OH typically has a HR increase >0.5 beats per minute per mmHg of SBP drop upon 3 min of active standing or tilt-table study [26]. Another is that nOH would not have physiological BP rise upon finishing the Valsalva maneuver, indicating impaired noradrenergic stimulation to the vessels [26]. Notably, nOH is debilitating due to impaired simple daily activities. It further confers an increased risk for hypercoagulable states, atrial fibrillation with cardioembolic stroke and structural heart diseases, and a higher risk for heart failure, neurodegenerative diseases, kidney failure, falls and fragility fractures and cognitive decline [27]. Actually, nOH has a much higher risk of all-cause mortality as a longitudinal study showed that the 10-year mortality rate in patients with nOH was over 60% [28]. Nevertheless, the diagnosis of nOH is rarely made, especially in individuals with diabetes. Poor awareness of this entity in individuals with diabetes across different specialties could be a major barrier.

As for managing DAN, optimizing glycemic control is always the first line treatment. Emerging evidence shows sodium glucose transporter 2 inhibitor (SGLT2i) presents a sympatho-homeostatic effect and potentially delays CAN. This consideration is based on the same target of renal tubular epithelial cells by SGLT2i and efferent sympathetic fibers promoting tubular sodium reabsorption [29], upregulated expression of SGLT2 in renal proximal tubule cells by noradrenaline [30], and the inhibition of tyrosine hydroxylase and noradrenaline by SGLT2i Dapagliflozin [31].

For symptomatic nOH, the goal is to minimize symptoms and increase autonomy in daily life. Non-pharmacological approaches and patient education of self-management are crucial including minimizing the medications impacting BP, correction of volume depletion by rapid drinking of 500 mL of water and moderate recumbent exercise and physical maneuvers. The

Fig. 2



Work model. Diabetic autonomic neuropathy (DAN) is involved in severe hypoglycemia events (SHEs) and impaired awareness of hypoglycemia (IAH), hypoglycemia-associated autonomic failure (HAAF) and cardiovascular autonomic neuropathy (CAN) with neurogenic orthostatic hypotension (nOH). DAN causes impaired glucagon response with sympathetic and sympathoadrenal response leading to SHEs/IAH. There is a reciprocal relationship between SHEs and IAH. DAN and the impacted hypothalamic–pituitary–adrenal (HPA) axis cause HAAF. The SHEs/IAH and HAAF compose a vicious cycle, which perpetuates itself and leads to exacerbated neuroglycopenic symptoms of hypoglycemia leading to severe SHEs-related events like coma and death. CAN, as a crucial component of DAN, has a wide spectrum of disorders. The nOH is debilitating and also links to the other adverse disorders of CAN, collectively leading to death-in-bed syndrome (DIB) and all-cause mortality.

standard protocol of medications is adrenergic agonists including midodrine in doses of 2.5 mg to 5 mg twice daily, fludrocortisone (0.1–0.4 mg) or Droxidopa (not available in many countries) [32]. Octreotide (50 µg three times daily subcutaneously) may be beneficial in patients with DAN and postprandial hypotension. Midodrine and fludrocortisone should be used cautiously in patients with supine hypertension and coronary artery disease [32].

Conclusion

DAN is a debilitating and fatal complication of DM. It affects multiple organs and is progressive. It emphasizes the importance of early recognition and individualized management of DAN, particularly its cardiac manifestations. Comprehensive autonomic testing, such as CARTs, plays a pivotal role in confirming the diagnosis and guiding therapeutic decisions. Tailored interventions, including advanced technologies like automated insulin delivery systems for T1D and pharmacotherapy targeting OH, can significantly improve patient outcomes and quality of life. These findings advocate for integrating advanced diagnostic and therapeutic strategies into clinical guidelines better to manage the cardiovascular complications associated with diabetes.

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C.W. and C.S. were involved in the conception and design. C.W., R.D., and A.Z. collected and analyzed pertinent literature and drafted the manuscript. S.K., O.A., and C.S. provided critical revision of the manuscript. All authors read and approved the final manuscript, and agreed to be accountable for all aspects of the work.

This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. It was approved by the ethics committee of Garden City Hospital.

Written informed consent was obtained from the patients.

Written informed consent was obtained from the patients for publication.

Conflicts of interest

There are no conflicts of interest.

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