CASE REPORT

Dulaglutide-induced cerebral venous thrombosis in a patient with type 2 diabetes mellitus

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Accepted 25 October 2018

SUMMARY

Though patients with diabetes mellitus are at a high risk of atherothrombotic events, every such event should not be attributed to the disease itself. We present a case of a patient with diabetes with headache and blurring of vision for 3 days. Brain imaging revealed right transverse sinus thrombosis and acute infarct of the right posterior parieto-occipital region, predominantly in the posterior cortical watershed zone. The patient was on subcutaneous dulaglutide for 3 weeks and was having nausea and vomiting. Various causes of cerebral venous thrombosis were ruled out with appropriate laboratory investigations. Finally, cerebral venous thrombosis was attributed to dulaglutide-induced nausea and vomiting which led to severe dehydration.

BACKGROUND

Patients with diabetes mellitus have a high probability of atherothrombotic catastrophe. Studies have shown a variety of diabetes mellitus-related abnormalities in haemostasis and thrombosis. Venous thrombosis has also been found to occur more frequently in diabetics.[1] The vascular endothelium is a primary site of defence against thrombosis and is abnormal in patients with diabetes mellitus. Cerebral venous thrombosis is an uncommon condition with a varied clinical presentation. The diagnosis is often delayed until imaging has been performed. Dulaglutide is a once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist that is approved for treatment of type 2 diabetes mellitus. The most common reported adverse events with dulaglutide are gastrointestinal disorders, particularly nausea, vomiting and diarrhoea. We report a case of a 52-year-old woman with dulaglutide-induced nausea and vomiting that caused cerebral venous thrombosis.

CASE PRESENTATION

A 52-year-old woman with diabetes mellitus presented to the emergency department with headache and blurring of vision since 3 days. On the review of her medical records, the patient was receiving dulaglutide 1.5 mg once a week and metformin 1000 mg twice a day. She was started on dulaglutide 0.75 mg once a week, 3 weeks previously which was subsequently increased to 1.5 mg after 2 weeks; though she had slight nausea and vomiting after initial doses. There was no history suggestive of similar episodes or other chronic illnesses like hypertension, asthma, epilepsy, tuberculosis or stroke. There was no history of trauma, haematological disorder like paroxysmal nocturnal haemoglobinuria, thrombotic thrombocytopenic purpura, sickle cell disease or polycythaemia, inflammatory bowel disease, sinusitis or intracranial infections, collagen vascular diseases like systemic lupus erythematosus, Wegener granulomatosis and Behcet syndrome, hepatic cirrhosis, sarcoidosis and nephrotic syndrome. There was no history of drug intake including oral contraceptives, steroids, erythropoietin, tamoxifen, thalidomide, L-asparaginase or heparin. There was no significant family history.

On examination, she was dehydrated with a pulse rate of 106/min and blood pressure of 94/58 mm Hg. There was no pallor, cyanosis, clubbing, pedal oedema or lymphadenopathy. On neurological examination, she was conscious, oriented to time, place and person. Visual acuity was 6/6, fundus examination revealed papilledema. Cranial nerves examination was normal. Superficial and deep tendon reflexes were normal. Plantar reflex was flexor. There was no neck rigidity. Examination of cardiovascular, respiratory and abdominal system was unremarkable.

INVESTIGATIONS

In blood investigations, complete haemogram revealed a haemoglobin of 13 g/dL with no evidence of sickle/atypical cells. Her plasma glucose was 204 mg/dL, serum Na^+140 mEq/L, serum k^+3.8 mEq/L, serum Cl^-108 mEq/L. Arterial blood gas analysis revealed pH 7.38 and HCO_3^-21.3 mmol/L. Calculated anion gap was 14.5 mEq/L. Her blood urea was 30 mg/dL and creatinine 0.8 mg/dL. Serum osmolality was 296.7 mOsm/kg. Urine examination was normal. Glycated haemoglobin (HbA1c) was 9.8%, suggestive of poor glycaemic control. Renal function and liver function tests were within normal limit. Prothrombin time was 14.8 s with international normalised ratio (INR) of 1.11.

- Thrombophilia profile: protein C 122% (70%–140%), protein S 81% (60%–130%), antithrombin III activity: 136.50% (80%–146.50%), factor V Leiden mutation, prothrombin gene mutation and MTHFR gene mutation was not detected.
- Antiphospholipid antibodies: anticardiolipin antibody 8.90 (<15 APL), beta-2 glycoprotein 1 IgG 2.61 (<20), beta-2 glycoprotein 1 IgM 7.81 (<20), lupus anticoagulant 50.40 (negative).
- Homocysteine 14.11 (5.38–16.20 μmol/L).

To cite: Rajput R, Pathak V, Yadav PK, *et al*. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2018-226346

ECG showed sinus tachycardia.

Imaging: Chest X-ray posterior-anterior view and ultrasound abdomen were normal. Non-contrast CT head was also normal. MRI brain showed acute infarct in the right parieto-occipital area. MR angiography showed no abnormality; however, MR venography showed mild attenuation and irregularity of flow-related enhancement of the right transverse sinus. T2-weighted fluid attenuated inversion recovery (T2W/FLAIR) images showed hyperintensity with diffusion restriction in the right posterior parieto-occipital region, predominantly in the posterior cortical watershed zone suggestive of acute infarct and right transverse sinus thrombosis.

DIFFERENTIAL DIAGNOSIS

- Cerebral oedema with increased intracranial pressure.
- Cerebral infarction.
- Cerebral venous thrombosis.
- Subarachnoid haemorrhage.

TREATMENT

She was diagnosed as a case of ischaemic stroke due to venous sinus thrombosis along with infarct. and she was treated with intravenous mannitol, low molecular-weight heparin along with intravenous fluids. Later on, she was shifted to oral anticoagulation and antiplatelet therapy. For the management of diabetes mellitus, she was given premixed insulin with glucose monitoring.

OUTCOME AND FOLLOW-UP

After 3 months of follow-up, she is doing well on premixed insulin, and her HbA1c is 7.3%. Her brain MR venogram on follow-up was normal.

DISCUSSION

Cerebral venous thrombosis having varied clinical manifestation is often missed and diagnosis delayed until imaging has been performed. Our case highlights this as the diagnosis was not made on the clinical ground alone as papilledema in our patient was the only clinical sign suggestive of raised intracranial pressure. Imaging confirmed the diagnosis of our patient. According to the history of the patient with her background of diabetes mellitus and her age, we considered different diagnoses like cerebral oedema with increased intracranial pressure, cerebral infarction, cerebral venous thrombosis and subarachnoid haemorrhage. Risk factors for cerebral venous thrombosis are those that affect blood stasis, changes in the vessel wall and changes to the composition of blood (Virchow triad). The common conditions associated with such abnormalities are pregnancy, puerperium, oral contraceptive use, head injury, dehydration, blood dyscrasia, malignancies, systemic diseases and inherited disorders. Usually, one or more risk factors can be identified in 85% of patients of cerebral venous thrombosis.[2]

Diabetics have a predisposition to present with dehydration, hyperosmolality, pH reduction and also have altered platelet, leucocyte functions along with dyslipidaemia. These factors lead to a microperfusion defect associated with endothelial damage. In settings of poor glycaemic control, all these elements further sweeten the kitty in establishing prothrombotic habitat.[3] Over and above, diabetes increases fibrinogen levels and decreases the mechanism of fibrinolytic activity with a decrease of tissue plasminogen activator, increases plasminogen activator inhibitor-l, increases concentrations of thrombin–antithrombin complexes, factor VIII activity and soluble tissue factor and alpha-2 macroglobulin levels. All of these factors establish a procoagulant status.[3] It is possible that during the episode of nausea and vomiting that the patient had a few weeks before, hyperosmolarity and hyperglycaemia and/or transient ketoacidosis might have occurred; however, this could not be verified as she was treated symptomatically for the symptoms outside, and no investigation was done at that time.

Our patient was screened for causes of cerebral venous thrombosis in which inherited causes were ruled out with appropriate laboratory investigations.

In our patient, the provocative factor for the cerebral venous thrombosis was dehydration which was due to nausea and vomiting 1 week before. Dehydration in the background of diabetes mellitus was 'a double-edged sword' which led on to the development of cerebral venous thrombosis in our patient and was due to dulaglutide-induced nausea and vomiting which was deduced from the history of the patient as the symptoms started with the initiation of dulaglutide.

Dulaglutide is a GLP-1 receptor agonist, a second-line, incretin-based diabetes treatment option. GLP-1 effects include increased insulin secretion, decreased glucagon release, increased satiety and slowed gastric emptying.[4] The most common adverse reactions to dulaglutide reported in 5% or more of patients include nausea, diarrhoea, vomiting, abdominal pain, decreased appetite, dyspepsia and fatigue.[5 6] The gastrointestinal disturbances are peculiar to GLP-1 analogue which are more on the first dose and are expected to lessen with succeeding doses. This can be troublesome to the magnitude of dehydration in few patients which, if not taken care of, can have serious consequences. With time, more data are expected to come to light which will further enhance our understanding of the effect profile of dulaglutide. Research Cardiovascular Events with a Weekly Incretin in Diabetes trial results, expected to be out in 2019, might throw more light on the safety profile of dulaglutide. A physician should have a vigil watch about the frequency and intensity of the symptoms of patients who are on dulaglutide. Studies have found that hyperglycaemia on admission is a strong predictor for poor clinical outcome in patients with cerebral venous thrombosis, even without a previous history of diabetes mellitus.[7] Although our patient had poor metabolic control (HbA1c 9.8%), she had less glycaemic variability. Whether strict glucose control can improve the outcome of these patients needs to be observed in future clinical trials.

Learning points

- Newer therapies for diabetes mellitus are having a better safety profile, but we should not be careless about even minor and known side effects-related symptoms.
- Minor symptoms if attended earlier can prevent serious adverse events.
- Dulaglutide can cause severe dehydration due to persistent nausea and vomiting.

Contributors RR is the guide and mentor under whose guidance this group is managing patients. New thought and curiosity are imbibed each time a patient is admitted for management. VP is senior resident who supervised the progress in the management of the patient and gave his inputs from time to time. PKY managed the patient and ensured that treatment is delivered on time and in proper form. SM helped in getting investigations done on time and ensured that these are least bothersome to the patient. We worked as a team and ensured that patient got the best possible treatment at lower cost.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Lemkes BA, Hermanides J, Devries JH, *et al*. Hyperglycemia: a prothrombotic factor? *J Thromb Haemost* 2010;8:1663–9.
2 Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med* 2005;352:1791–8.
3 Carl GF, Hoffman WH, Passmore GG, *et al*. Diabetic ketoacidosis promotes a prothrombotic state. *Endocr Res* 2003;29:73–82.
4 Scheen AJ. GLP-1 receptor agonists or DPP-4 inhibitors: how to guide the clinician? *Ann Endocrinol* 2013;74:515–22.
5 Nauck M, Weinstock RS, Umpierrez GE, *et al*. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). *Diabetes Care* 2014;37:2149–58.
6 *Trulicity (dulaglutide) prescribing information Indianapolis*. Indiana: Eli Lilly and Company.
7 Zuurbier SM, Hiltunen S, Tatlisumak T, *et al*. Admission hyperglycemia and clinical outcome in cerebral venous thrombosis. *Stroke* 2016;47:390–6.