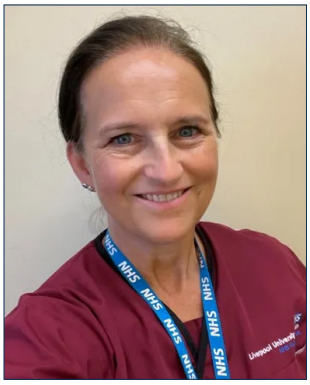
Diagnostic dilemma – dealing with uncertainty

In cases where a diagnosis of type 1 diabetes is uncertain, it can usually be confirmed by testing for autoantibodies. There are three main antibodies that can be tested clinically to inform whether a person is likely to have type 1 diabetes: GAD, IA2 and ZnT8. Levels of these antibodies can, however, be affected by the duration of diabetes, age of the individual and other autoimmune conditions. Diagnosis of any type of diabetes relies not only on results from such tests, but also on an accurate and extensive clinical history and examination.



Julie Brake
Diabetes Nurse Consultant, Royal Liverpool University Hospital NHS Trust

Citation: Brake J (2024) Diabetes Portrait: Diagnostic dilemma – dealing with uncertainty. *Journal of Diabetes Nursing* **28**: JDN354

Case presentation

Mr A is a 42-year-old man with type 2 diabetes, which was diagnosed 14 years earlier, in 2010. He has been referred from a consultant clinic to the diabetes nurses for follow-up owing to high HbA_{1c} (119 mmol/mol). He also has proliferative retinopathy and maculopathy, and is under the care of a specialist eye team.

He was treated initially with metformin, but it was not tolerated. Currently, he is on gliclazide 80 mg twice daily. Dapagliflozin 10 mg has been started recently. He feels better and his blood glucose level has improved.

Mr A lives with wife and children. His grandfather had diabetes. He is experiencing left wrist pain and muscle spasms in his left arm, and has also been diagnosed with a frozen shoulder.

Tests for markers of type 1 diabetes have been conducted recently: GAD, >2000 U/mL; IA2 and ZnT8 were negative. C-peptide, 1481 pmol/L (normal range, 190–990 pmol/L) was indicative of type 2 diabetes.

Type 1 diabetes autoantibody ranges

Autoantibody	Normal range (positivity threshold), U/mL
GAD	0–10.9 (≥11.0)
IA2	0–7.4 (≥7.5)
ZnT8	0–9.9 (≥10.0) (aged ≥30 years)

Indications for diabetes in Mr A

Type 1	Type 2
Raised GAD	Diagnosed >10 years On oral hypoglycaemic agents
	BMI, 32 kg/m^2
	Raised serum C-peptide
	Family history
	Weight stable

Mr A was referred to the diabetes nursing team for insulin initiation because of his high blood glucose level and raised GAD level. He was started on a basal insulin analogue, 8 units once daily, titrated up according to glucose levels. His HbA_{1c} is currently 67 mmol/mol.

While Mr A's GAD measurement was over the maximum recordable level (suggestive of type 1 diabetes), all other signs and his history indicated type 2 diabetes. An online search was conducted to look for any other possible cause of the very high GAD reading.

Information indicated a possible link to stiff-person syndrome (SPS), a rare neurological disease. Further reading suggested that the Mr A's joint pain and muscle spasm and weakness could be further mild symptoms of SPS. He attended a further appointment to assess any other symptoms that

could be linked to the condition. Thereafter, he was referred to neurology for further review.

Neurology review

On examination, there were no further symptoms of SPS, although deep tendon reflexes were diminished and his neurosensory pattern was impaired distally. However, the neurologist felt this was due to Mr A's diabetes and he was discharged from neurology.

What is stiff-person syndrome?

Stiff-person syndrome is a rare, progressive and disabling disorder of the central nervous system. It is immune-mediated and often under-diagnosed. Symptoms may include:

- Stiff muscles in the torso, arms and legs.
- A greater sensitivity to noise, touch and emotional distress, which can set off muscle spasms.

Over time, people with SPS may develop hunched-over postures. Some may become too disabled to walk or move. Because people with SPS do not have the normal reflexes to catch themselves, many have recurrent falls. They may become too afraid to leave their homes, as noises can trigger spasms and falls.

SPS affects twice as many females as males (Baizabal-Carvallo et al, 2015). The stiffness is due to the simultaneous activation of agonist and antagonist muscles. Depression and anxiety often accompany the disorder, and it can be misdiagnosed as a psychiatric illness (Buechner, 2015). Other neurological symptoms include nystagmus (rapid, uncontrollable eye movements), increased reflexes and paroxysmal dysautonomic crisis (Baizabal-Carvallo, 2015).

SPS is frequently associated with other autoimmune diseases, including type 1 diabetes. Its cause is not yet understood, but research indicates that it is the result of an autoimmune reaction in which nerve cells in the central nervous system that control muscle movement are attacked.

Diagnosing SPS

Most people with SPS have greatly elevated levels of GAD antibodies. These levels are at least 10 times above the range seen in type 1 diabetes (which are themselves up to 10 times above normal).

Reaching a diagnosis for SPS can be difficult and requires a high index of suspicion. There are no accepted criteria, currently. The significant features that increase the suspicion are:

- Stiffness in the limb and axial muscles, resulting in impairment of ambulation.
- Presence of spasms that are precipitated by movements, noises or emotional upset.
- Positive response to diazepam.
- Continuous motor unit activity on electromyography (EMG), which is suppressed with diazepam.
- Lack of other neurological signs that point to a different diagnosis (Dalakas, 2009).

Treating SPS

There is no cure for SPS but, with appropriate treatment, symptoms may be relieved. Several symptoms improve with oral diazepam (an anti-anxiety and muscle-relaxant drug) or with drugs that alleviate muscle spasms, such as baclofen or gabapentin.

Case outcome

Following the investigations, close monitoring and discussion of his case within the multidisciplinary team, Mr A still has a diagnosis of type 2 diabetes. He is aware of the diagnosis, and has been given the appropriate advice and information to self-manage his condition.

Key learning points

- Be enquiring and question presentations, particularly if something does not indicate the expected diagnosis.
- If an investigation does not fit the clinical picture, conduct some research and discuss with the case with colleagues at a multidisciplinary team meeting.
- Be open to new theories and knowledge.
- Ensure safety-netting advice is provided to the person with diabetes during times of uncertain diagnosis.
- Ensure clear documentation of plans, investigations and discussions for any individual with an uncertain diagnosis.

References

Baizabal-Carvallo JF, Jankovic J (2015) Stiff-person syndrome: insights into a complex autoimmune disorder. *J Neurol Neurosurg Psychiatry* **86**: 840–8

Buechner S, Florio I, Capone L (2015) Stiff person syndrome: a rare neurological disorder, heterogeneous in clinical presentation and not easy to treat. *Case Rep Neurol Med* **2015**: 278065

Dalakas MC (2009) Stiff person syndrome: advances in pathogenesis and therapeutic interventions. *Curr Treat Options Neurol* **11**: 102–10