INTRODUCTION

In daily clinical practice, we are inclined to classify the type of diabetes individual patients have as one type. A patient with HNF1A-MODY and also positive for GAD-65 autoantibodies is presented.

In clinical practice, diabetes is mainly categorized into two main types, type 1 diabetes (T1D) or type 2 diabetes (T2D), along with some more rare or uncommon forms (see below).

Type 1 diabetes is an autoimmune disease with the presence of autoantibodies, i.e., against the insulin-producing β-cell antigen GAD-65, which eventually leads to insulinopenia due to rapid destruction of β-cells. Type 1 diabetes was previously called juvenile diabetes based on the incidence of the disease being highest at these ages. However, T1D may unfold at any age.

Type 2 diabetes is more of a cardiovascular lifestyle disease where lack of exercise and excess calories lead to visceral obesity with concomitant insulin resistance that in genetically predisposed individuals result in overt diabetes. Type 2 diabetes was previously called elderly onset diabetes based on the incidence of the disease being highest at these ages. However, T2D may unfold at any age.

Type 2 diabetes is more of a cardiovascular lifestyle disease where lack of exercise and excess calories lead to visceral obesity with concomitant insulin resistance that in genetically predisposed individuals result in overt diabetes. Type 2 diabetes was previously called elderly onset diabetes based on the incidence of the disease being highest at these ages. However, T2D may unfold at any age.

Type 2 diabetes is more of a cardiovascular lifestyle disease where lack of exercise and excess calories lead to visceral obesity with concomitant insulin resistance that in genetically predisposed individuals result in overt diabetes. Type 2 diabetes was previously called elderly onset diabetes based on the incidence of the disease being highest at these ages. However, T2D may unfold at any age.
against the β-cell antigen GAD-65 (449 U/mL [ref. <5]) but—and surprisingly—he had positive titers of IgG antibodies.

Patients with HNF1A-MODY have an increased risk of adenomatosis of the liver.10 However, ultrasound examination of the liver showed no abnormality.

3 | DISCUSSION

3.1 | HNF1A-MODY

Maturity-Onset Diabetes of the Young accounts for only 3%-4% of all diabetes in the Western world. HNF1A-MODY (previously called MODY-3) is a predominant form of monogenic diabetes and is caused by mutations in the transcription factor HNF-1α.11,12 Because HNF-1α is very important for the β-cell functional differentiation and growth as well as its ability to synthesize and release insulin, mutations in this transcription factor lead to defective insulin secretion.12 However, it often takes a long time before overt diabetes is diagnosed, asmutations in HNF-1α compensatory downregulate the expression of SGLT-2 in the kidneys.4 This causes a lowered kidney threshold with increased glucosuria, which lowers glycemia. The same mechanism is used by the latest class of antidiabetic drugs, SGLT-2 inhibitors.

3.2 | Double diabetes

The patient in this paper shows evidence of two types of diabetes, a congenital monogenic type (HNF1A-MODY) and an acquired autoimmune type directed against a known β-cell antigen (GAD-65). This is an unexpected and surprising finding, as HNF1A-MODY and autoimmune diabetes do not have much pathogenic mechanisms in common in β-cell dysfunction. The mutation in HNF-1α results in defective insulin secretion whereas the autoimmune process results in apoptotic cell death, two completely different mechanisms. The extent to which the autoimmune process has contributed to the patient’s poor insulin production is impossible to say but will be monitored over time and we are also evaluating whether GLP-1-based therapy can slow down or reverse this. It is likely, however, that he will need to continue with insulin in some form. A few (1%-2%) of nondiabetic people has GAD-65 antibodies without ever getting diabetes. However, antibody titers in such cases are usually much lower than the level in the current case.

It is very difficult to prove if, or to what extent, the autoimmunity in this patient—albeit fairly strong—has contributed to his diabetes and impaired insulin secretion. Nonetheless, in a study of 77 individuals with long-duration HNF1A-MODY the lowest C-peptide level was 0.36 nmol/L,13 thus higher than in the present patient. This lends support to the notion that the autoimmunity contributed to the patient’s impaired insulin secretion.
The coexistence of monogenic and autoimmune diabetes is unusual, but not unique. Anecdotal case reports have been published, as well as more systematic reviews. In a Czech material, about 30% of HNF1A-MODY patients were also positive for antibodies to GAD-65, whereas only 1% in a British study and 15%-20% in a Scandinavian report. Coexistence of biomarkers for autoimmune diabetes and types of monogenic diabetes other than HNF1A-MODY has also been described. Interestingly, an SNP (rs2650000) in the gene for HNF-1α has been shown to predispose to autoimmune diabetes.

In daily clinical practice, we are inclined to classify the type of diabetes individual patients have as one type, but in recent years the concept of “double diabetes” has received increased attention in the scientific literature. This is not least due to the fact that overweight and obesity are increasingly abundant in large parts of the world and also affect patients with T1D. Of course, having T1D does not provide protection against getting abdominal obesity and consequent insulin resistance, a cardinal finding in T2D. Thus, many patients with T1D in fact also have T2D with the cardiovascular risk factor burden the latter entails. In most studies, ”double diabetes” is defined as T1D combined with the metabolic syndrome. ”Double diabetes” is, however, not an established concept but herein refers to diabetes which is caused by two completely different mechanisms of action. The frequency of the comorbidity varies; in a German material it was about 25% and individuals with ”double diabetes” showed a greatly increased risk of both microvascular and macrovascular complications compared to T1D, independent of glucose control, finding essentially similar to that in a subgroup analysis of the DCCT study. Recently, a Swedish study showed that increasing BMI in male T1D patients is associated with an increased risk of mortality, cardiovascular disease, and heart failure. It has also been reported that obesity and insulin resistance can interact with the immune system and thus aggravate the autoimmune attack.

Finally, a case description shows that one can also have triple diabetes: HNF1A-MODY with T1D and the metabolic syndrome.

The take home message of this case report is that one thing does not exclude another (or a third), something to keep in mind not least in the event of an unexpected deterioration in glycemic control.

CONFLICT OF INTEREST
Å.S. has received lecture and consultancy fees from Boehringer-Ingelheim, Novo-Nordisk, MSD, Sanofi, Pfizer and Astra-Zeneca.

AUTHOR CONTRIBUTIONS
ÅS provided care for the patient, researched data, wrote the manuscript, and edited/reviewed the manuscript. ÅS is the guarantor of this work and, as such, had full access to all the data in the case presentation and literature review and takes responsibility for the integrity of the information presented.

ETHICS APPROVAL
The patient gave informed consent to this publication.

DATA AVAILABILITY STATEMENT
Data are available in the patient’s medical record.

ORCID
Ake Sjöholm https://orcid.org/0000-0002-5274-9748

REFERENCES
1. Thomas NJ, Lynam AL, Hill AV, et al. Type 1 diabetes defined by severe insulin deficiency occurs after 30 years of age and is commonly treated as type 2 diabetes. Diabetologia. 2019;62(7):1167-1172.
2. Hattersley AT, Patel KA. Precision diabetes: learning from monogenic diabetes. Diabetologia. 2017;60(5):769-777.
3. Yang Y, Chan L. Monogenic diabetes: what it teaches us on the common forms of type 1 and type 2 diabetes. Endocr Rev. 2016;37(3):190-222.
4. de Santana LS, Caetano LA, Costa-Riquetto AD, et al. Targeted sequencing identifies novel variants in common and rare MODY genes. Mol Genet Genomic Med. 2019;7(12):e962. https://doi.org/10.1002/mgg3.962.
5. Farilla L, Bulotta A, Hirshberg B, et al. Glucagon-like peptide 1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. Endocrinology. 2003;144(12):5149-5158.
6. Fehse F, Trautmann M, Holst JJ, et al. Exenatide augments first- and second-phase insulin secretion in response to intravenous glucose in subjects with type 2 diabetes. J Clin Endocrinol Metab. 2005;90(11):5991-5997.
7. Urakami T, Habu M, Okuno M, Suzuki J, Takahashi S, Yorifuji T. Three years of liraglutide treatment offers continuously optimal glycemic control in a pediatric patient with maturity-onset diabetes of the young type 3. J Pediatr Endocrinol Metab. 2015;28(3-4):327-331.
8. Østoft SH, Bagger JI, Hansen T, et al. Glucose-lowering effects and low risk of hypoglycemia in patients with maturity-onset diabetes of the young when treated with a GLP-1 receptor agonist: a double-blind, randomized, crossover trial. Diabetes Care. 2014;37(7):1797-1805.
9. Docena MK, Fairman C, Stanley CM, Pantalone KM. Mody-3: novel HNF1A mutation and the utility of glucagon-like peptide (GLP)-1 receptor agonist therapy. Endocr Pract. 2014;20(2):107-111.
10. Haddouche A, Bellanne-Chantelot C, Rod A, et al. Liver adenomatosis in patients with hepatocyte nuclear factor-1 alpha maturity onset diabetes of the young (HNF1A-MODY): clinical, radiological and pathological characteristics in a French series. J Diabetes. 2020;12(1):48-57.
11. Yamagata K, Oda N, Kaisaki PI, et al. Mutations in the hepatocyte nuclear factor-1alpha gene in maturity-onset diabetes of the young (MODY3). Nature. 1996;384(6608):455-458.
12. Lehto M, Tuomi T, Mahtani MM, et al. Characterization of the MODY3 phenotype. Early-onset diabetes caused by an insulin secretion defect. *J Clin Invest*. 1997;99(4):582-591.

13. Perkins BA, Lovblom LE, Lanciöt SO, Lamb K, Cherney DZI. Discoveries from the study of longstanding type 1 diabetes. *Diabetologia*. 2021. https://doi.org/10.1007/s00125-021-05403-9

14. Maltoni G, Zucchini S, Scipione M, Mantovani V, Salardi S, Cicognani A. Onset of type 1 diabetes mellitus in two patients with maturity onset diabetes of the young. *Pediatr Diabetes*. 2012;13(2):208-212.

15. Lindgren CM, Widén E, Tuomi T, et al. Contribution of known and unknown susceptibility genes to early-onset diabetes in Scandinavia: evidence for heterogeneity. *Diabetes*. 2002;51(5):1609-1617.

16. Urbanová J, Rypáčková B, Procházková Z, et al. Positivity for islet cell autoantibodies in patients with monogenic diabetes is associated with later diabetes onset and higher HbA1c level. *Diabet Med*. 2014;31(4):466-471.

17. McDonald TJ, Colclough K, Brown R, et al. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from type 1 diabetes. *Diabet Med*. 2011;28(9):1028-1033.

18. Andersen MK, Sterner M, Forsén T, et al. Type 2 diabetes susceptibility gene variants predispose to adult-onset autoimmune diabetes. *Diabetologia*. 2014;57(9):1859-1868.

19. Merger SR, Kerner W, Stadler M, et al. Prevalence and comorbidities of double diabetes. *Diabetes Res Clin Pract*. 2016;119:48-56.

20. Cleland SJ. Cardiovascular risk in double diabetes mellitus—when two worlds collide. *Nat Rev Endocrinol*. 2012;8(8):476-485.

21. Kilpatrick ES, Rigby AS, Atkin SL. Insulin resistance, the metabolic syndrome, and complication risk in type 1 diabetes: “double diabetes” in the diabetes control and complications trial. *Diabetes Care*. 2007;30(3):707-712.

22. Kietsiriroje N, Pearson S, Campbell M, Ariëns RAS, Ajan RA. Double diabetes: a distinct high-risk group? *Diabetes Obes Metab*. 2019;21(12):2609-2618.

23. Edqvist J, Rawshani A, Adiels M, et al. BMI, mortality, and cardiovascular outcomes in type 1 diabetes: findings against an obesity paradox. *Diabetes Care*. 2019;42(7):1297-1304.

24. Redondo MJ, Evans-Molina C, Steck AK, Atkinson MA, Sosenko J. The influence of type 2 diabetes-associated factors on type 1 diabetes. *Diabetes Care*. 2019;42(8):1357-1364.

25. Bowden SA, Hoffman RP. Triple diabetes: coexistence of type 1 diabetes mellitus and a novel mutation in the gene responsible for MODY3 in an overweight adolescent. *Pediatr Diabetes*. 2008;9(2):162-164.

How to cite this article: Sjöholm Å. GAD-65 antibodies in a case of HNF1A-Maturity-Onset Diabetes of the Young: Double diabetes?. *Clin Case Rep*. 2021;9:e04151. https://doi.org/10.1002/ccr3.4151