GLYCEMIC CONTROL IN A TYPE 1 DIABETES PATIENT WITH SERONEGATIVE AUTOIMMUNE HEPATITIS

Nicoleta MÎNDRESCU1, Georgeata VĂCARU2, Diana Loreta PĂUN3, Rucsandra DĂNCIULESCU MIULESCU3,4 and Loreta GUJA3

1 Nicodiab Private Practice, Bucharest,
2 EasyDiet Private Practice, Bucharest
3 "Carol Davila" University of Medicine and Pharmacy, Bucharest
4 "N.C.Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases Bucharest

Corresponding author: Dănciulescu Miulescu Rucsandra, rucsandra_mi@yahoo.com

Accepted September 12, 2018

Type 1 diabetes mellitus (T1DM) has been associated with other autoimmune diseases especially celiac disease and autoimmune thyroiditis. T1DM and autoimmune hepatitis (AIH) is a rare association. We describe the case of a young man with T1DM who developed sclero-tegumentary jaundice due to a seronegative AIH. The patient was treated for diabetes with basal bolus insulin therapy. When he was put into hospital in Fundeni Institute the values of glycated hemoglobin (HbA1c) were between 7-7.5%. Treatment of AIH included corticosteroids and azathioprine. It is known that glucocorticoid therapy generates increased glycemic values by impairment of multiple pathways. Insulin doses have undergone significant increases when given this treatment—basically, the total insulin dose increased 3-fold. This case indicates that AIH can occur in young T1DM patients and under these conditions glycemic control requires a constant, even significant adjustments of insulin doses.

Keywords: type 1 diabetes mellitus, autoimmune hepatitis, glycemic control.

INTRODUCTION* Type 1 diabetes mellitus (T1DM) can be associated with other autoimmune diseases especially celiac disease and autoimmune thyroiditis (in children and adult subjects). T1DM and AIH are rarely associated. The pathogenesis of co-occurrence between different autoimmune diseases is not fully clarified. A genetic predisposition of both diseases has been suggested, because they are associated with human leukocyte antigen (HLA) DR3 and DR4. Genetic predisposition, associated with environmental triggers can lead to the activation of some factors, which subsequently initiates abnormal immune response. AIH is a a chronic progressive liver disease characterized by an important inflammatory process. AIH is classified as type 1, 2 or type 3 according to different autoantibodies. Type 1 AIH is characterized by the presence of antinuclear antibodies (ANA) and/or smooth muscle autoantibodies (SMA), type 2 by antibodies to soluble liver antigen (SLA). In very rare cases, patients do not show autoantibodies markers and diagnosis is based only on clinical, biochemical and histological criteria.

GENERAL CONSIDERATIONS The incidence of the AIH is around 1–2 per 100,000 people per year. There is a variation in incidence in different countries which suggests differences in risk factors for this disease. The disease has a strong female predominance with the main interest a young and middle aged women, with a peak in childhood3. The clinical presentation includes fulminant liver failure, acute and chronic hepatitis, cirrhosis or hepatocellular carcinoma. The diagnosis of AIH is based of elevated transaminases and immunoglobulin G (IgG) levels, typical autoantibodies and liver biopsy. Criteria for the diagnosis of AIH were formulated in 1993 and revised in 1999. The criteria
include the following parameters: female gender, alanine aminotransferase (ALT): aspart aminotransferase (AST) ratio, serum globulins or IgG levels, ANA, SMA or LKM-1, anti-mitocondrial antibody (AMA), hepatitis viral markers, drug history, average alcohol intake, liver histology, optional parameters: seropositivity for other defined autoantibodies, HLA DR3 or DR4, response to therapy. A pretreatment score of 10 points or higher probably indicates AIH and a score pretreatment of 15 points definitely indicates AIH. In 2008 International Autoimmune Hepatitis Group developed simplified criteria for the diagnosis of this disease using four parameters: autoantibodies markeres, immunoglobulins levels, exclusion of viral hepatitis and histology. Authors propose the diagnosis of probable AIH at a 6 points score or greater and definite AIH at 7 points score or higher.

Treatment of AIH in children has no particularities compared to adults except the high doses of corticosteroids used due to the more aggressive evolution of affection in this age group. The goal of therapy is to achieve and maintenance complete remission and prevention of disease progression. Prednisone or prednisolone (in equivalent doses) in monotherapy or in combination with azathioprine is the first-line AIH treatment. In monotherapy the initial recommended Prednisolone dose is 1 mg/kg of body weight; in combination with azathioprine (50 mg/day) the dose of glucocorticoids will be reduced to about 1/2 of the previously mentioned dose. The dose of glucocorticoids should be gradually reduced; rapid reduction is a risk factor for recurrence. Treatment should be continued until the ALT, AST, IgG, total bilirubin (BT), gamma glutamil transferase (GGT) and liver tissue have become normal. In patients who do not tolerate prednisone, prednisolone or azathioprine or not respond to standard treatment, administration of cyclosporine, methotrexate, tacrolimus or mycophenolate motefil can be considered. Liver transplantation is recommended in patients with acute liver failure unresponsive to immunosuppressive treatment.

**CASE REPORT**

A young man (13-year-old) diagnosed with T1DM when he was 4 years old was hospitalized in the Fundeni Clinical Institute for physical asthenia, sclero-tegumentary icter and elevated liver enzymes for about 8 months (2017). As diabetes treatment the patient was receiving a basal bolus insulin therapy (rapid acting insulin analogue 21 U/day and long acting basal insulin analogue- 18 U/day). The patient and his family denied any alcohol and drugs consumption with potential liver toxicity. There was no family history of autoimmune disorders. Physical examination during the hospitalization in Fundeni Institute revealed: height 163 cm, weight 44 kg, sclero-tegumentary jaundice and palpable liver at 3 cm below the coastal rib. Viral serologies for hepatitis (hepatitis B and C), conventional serologies for autoimmune hepatitis (ANA, SMA, anti-LKM-1), toxicological tests and specific tests for Wilson’s disease were negative. Infections with cytomegalovirus and Epstein-Barr virus were excluded. Investigations revealed severe hepatocitolyis (ALT: 1047 U/l, AST: 1154 U/l), cholestasis (BT: 9.4 mg/dl, direct bilirubin-BD: 8.8 mg/dl, GGT: 87 U/l), hypoalbuminemia (3.3 g/dl), leukopenia (2000/mm3), neutropenia (15/mm3) and thrombocytopenia (141.000/mm3), high titer of immunoglobulin G (IgG: 3030 mg/dl) and clotting abnormalities (fibrinogen 171 mg/dl, international normalized ratio-INR 1.39). Abdominal ultrasound has been performed and highlighted hepatomegaly with homogeneous structure, hileous liver adenopathy, minimal ascites. Ultrasound guided biopsy of the liver followed by histopathological examination showed moderate portal and lobular hepatitis, cholestatic “in the bridge” fibrosis and tendency to micronodulum formation.

Therapy was initiated including polyunsaturated phospatidyl-choline 2U/day, human albumin 20% 100ml/day, protective antibiotic therapy due to neutropenia and diuretic. Insulin doses were adjusted, and the correction of elevated blood glucose values was performed. Dynamically, clotting tests improved on established therapy, but liver enzymes remained elevated reaching a maximum of ALT 2108 U/l and AST 1148 U/l. According to the Scoring System of the International Autoimmune Hepatitis Group, the patient presents a pretreatment score of 17 points which allows the diagnosis of serum negative autoimmune hepatitis. The specific therapy was initiated: prednisone 30 mg/day with gradual reduction of this dose; initial administration of azathioprine was delayed due to neutropenia. 2 weeks after initiation of corticotherapy, immunosuppressive therapy was associated (50 mg/day azathioprine). Treatment was closely monitored with the periodic determination of liver biochemistry, and hemolecogram. Dynamics of liver enzymes are shown in table I. Currently, the patient is being treated with prednisone 15 mg/day, azathioprine 100 mg/day, insulin aspart 63 U/day, insulin detemir 48 U/day, spironolactone 100 mg/day.
Glycemic control in a type 1 diabetes patient with seronegative autoimmune hepatitis

Table 1
Dynamics of liver enzymes

<table>
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<th>July 2017</th>
<th>July 2017</th>
<th>August 2017</th>
<th>October 2017</th>
<th>November 2017</th>
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<td>295</td>
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<tr>
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<td>1148</td>
<td>59</td>
<td>158</td>
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</tr>
</tbody>
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**DISCUSSION**

The association between T1DM and AIH is very rare. Using the PubMed database with the keywords “autoimmune hepatitis” and “type 1 diabetes”, we have identified 64 items. After the removal of the reports on other disease, 12 publications were found.

The patient was diagnosed with T1DM when he was 4 years old and followed basal bolus insulin therapy with dose adjustments based on glycemic values, carbohydrates and exercise. At the admission in Fundeni Institute the values of HbA1c were in targets: 7–7.5%. It is worth mentioning that blood glucose and HbA1C goals for children and adolescents with T1DM according to American Diabetes Association are: blood glucose before meals 90–130 mg/dl, bedtime/overnight 90–150 mg/dl, HbA1c < 7.5%.16 It is known that glucocorticoid therapy generates increased glycemic values by impairment of multiple pathways including beta cell dysfunction and insulin resistance17. Insulin doses have undergone significant increases on the background of this treatment-basically, the total insulin dose increased 3-fold but the last value of Hba1c was 8.1%.

The onset of AIH in the presented case was acute. Treatment with corticosteroids was initiated early with 30 mg prednison/day. The dose chosen was a small one due to the hyperglycemic effect of prednisone. Studies have highlighted that treatment with corticosteroids induces clinical, laboratory and histological remission in 80% of patients with AIH within 3 years18,19. Glucocorticoid treatment generates side effects in approximately 13% of patients, incomplete response in 13% of patients and treatment failure in 9%. After drug withdrawal relapse appears in a percentage of 50%-86%20.

The addition of azathioprine allows the steroids dose reduction and it is used in the long term for disease control. Azathioprine in monotherapy is continued in the remission period. Initial azathioprine dose is 1 mg/kg of body weight and is titrated depending on the response to therapy. The maximum dose is 200 mg/day but usually patients respond to 100 mg/day21.

Treatment decisions in AIH associated with T1DM must take into account the international recommendations, but as Czaja AJ says in a review published in 2010 in World Journal of Gastroenterology, “clinical judgment remains the essence of successful therapy”20.

**CONCLUSION**

This case indicates that seronegative AIH can occur in young T1DM patients and under these conditions glycemic control requires a constant, even significant adjustments of insulin doses.

**REFERENCES**


