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Case Report

Co-existence of Type 1 Diabetes Mellitus and Myasthenia Gravis: A Case Report and Review of the Literature

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ABSTRACT

Background/Objective: Type 1 diabetes (T1D) and myasthenia gravis (MG) are autoimmune conditions that rarely co-occur. Here, we report a child with MG who subsequently developed T1D.
Case report: An 11-year-old girl with seropositive MG diagnosed at 4 years of age presented with muscle pain, cramps, and weight loss of 3.5 kg over 4 months. Her MG was in remission on daily pyridostigmine. She denied polyuria, polydipsia, recent illnesses, or other medications. She was prepubertal and had stable vitals with normal systemic examination. Initial work up for a probable diagnosis of rhabdomyolysis showed hyperglycemia and glucosuria. She had ketosis without acidosis. Diabetes autoantibodies were positive (anti-glutamic acid decarboxylase antibody 113.5 IU/mL (reference range < 5 IU/mL), anti-zinc transporter 8 antibody > 500 U/mL (reference range < 15 IU/mL)). Screening for autoimmune thyroid disease and celiac disease was negative. Patient was diagnosed with T1D and was started on subcutaneous insulin.
Discussion: The co-existence of MG and T1D is rare. All the 4 prior reported patients from Europe were diagnosed with T1D prior to or concurrently with MG. In contrast, our patient was first diagnosed with MG and subsequently diagnosed with T1D 7 years later.
Conclusions: Consider screening for T1D in patients with MG and offering treatment to those above 8 years and older with stage 2 T1D to delay its onset. Along with other causes, T1D should also be considered when patients with MG present with nonspecific symptoms such as fatigue and weight loss.

Introduction

Type 1 diabetes mellitus (T1D), one of the most common autoimmune conditions in youth, results from autoimmune beta cell destruction leading to absolute insulin deficiency. Individuals with T1D are at increased risk for other autoimmune diseases with autoimmune thyroid disease and celiac disease being the most common. Other autoimmune conditions associated with T1D include primary adrenal insufficiency, autoimmune hepatitis, autoimmune gastritis, dermatomyositis, and rarely myasthenia gravis (MG).[1] MG is an autoimmune disease in which antibodies are directed against the acetyl choline receptor or receptor related proteins in the postsynaptic membrane of the neuromuscular junction. Antibody mediated interruption of acetyl choline action leads to fluctuating levels of muscle weakness involving ocular, bulbar, limb and/or respiratory muscles.[2] There have been 5 previous reports of the co-occurrence of T1D and MG in children below 18 years. In all but one report, MG was either diagnosed after or concurrently with T1D (Table 1). [2-6] Here, we report a child with a history of MG who subsequently developed T1D.

Case Report

An 11-year-old female presented to the emergency department with severe muscle pain and muscle cramping that started suddenly while playing in the grounds with her friends. She denied

Abbreviations: AIRE, auto-immune regulator; BACH2, BTB domain And CNC homolog 2; FOXP3, Forkhead Box P3; HLA, human leukocyte antigen; MHC, major histocompatibility complex; MG, myasthenia gravis; PTPN22, protein tyrosine phosphatase nonreceptor type 22; T1D, type 1 diabetes.

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history of trauma or injury. There was no history of fever, muscle swelling or weakness.

Examination revealed an alert child with blood pressure of 112/73 mm Hg, respiratory rate of 24 breaths per minute. She was afebrile. Her weight was 28.7 kg (eighth percentile based on CDC growth chart) which was decreased from 32.4 kg 4 months earlier. Her body mass index (BMI) had also decreased from 18.1 kg/m^2 to 15.8 kg/m^2. She had Tanner I breast and pubic hair. There was no localized tenderness or weakness of the extremities. She had no thyromegaly. The remainder of her examination was normal.

Initial urine analysis and metabolic work up for a probable diagnosis of rhabdomyolysis were suggestive of hyperglycemia and glucosuria leading to further detailed work up that confirmed a diagnosis of T1D (Table 2). She denied polyuria, polydipsia, polyphagia, or nocturia. The patient was started on a basal bolus subcutaneous insulin regimen.

The patient had been diagnosed with MG 7 years earlier at age 4 years when she presented with 1 month of progressive ptosis. At that time, she had positive muscle acetyl choline receptor binding antibody (0.20 nmol/L (normal $\leq$ 0.02 nmol/L)) and modulating antibody (71% (normal 0% to 20%)). Computed tomography was negative for thymoma. At the time of her presentation with hyperglycemia, her MG had been in remission on pyridostigmine for more than a year. There was no history of recurrent infections requiring hospitalizations in the past. She had normal development.

Her parental lineage ethnic background was Cape Verdean. There was no family history of T1D, MG or other autoimmune conditions.

Our patient was doing well on her last follow up in terms of diabetes control with a hemoglobin A1c of 7.8% on a basal bolus insulin regimen. Her total insulin dose is 0.3 units/kg/d.

Discussion

Autoimmune diseases affect 3% to 5% of the general population. The development of autoimmune conditions is thought to be caused by an environmental trigger in a genetically susceptible individual. Genetic susceptibility can come in the form of major histocompatibility complex (MHC) gene variants encoding proteins involved in antigen presentation, genes engaged in innate and adaptive immunity (ie, protein tyrosine phosphatase non-receptor type 22 (PTPN22), BTB domain And CNC homolog 2 (BACH2), auto-immune regulator (AIRE) gene, and Forkhead Box P3 (FOXP3) gene), or via epigenetic mechanisms (ie, methylation, acetylation, ubiquitination and phosphorylation). Each of these mechanisms has been implicated in the development of specific autoimmune diseases. Genetic susceptibility likely explains the occurrence of multiple autoimmune diseases within one individual as well as the increased risk of an autoimmune disease in other family members.[7]

Impaired immunologic tolerance can also induce different autoimmune diseases. Regulatory T cell dysfunction leading to failure of peripheral immunologic tolerance may play a role in the development of T1DM based on animal studies.[5] Our patient was an otherwise healthy child with no history of recurrent infections. She had normal immunoglobulin A levels.

Ocular MG involving only the extra-ocular muscles, as in our patient, accounts for 10% to 35% of cases of MG, and is more

Highlights

- A prepubertal girl with type 1 diabetes (T1D) and myasthenia gravis (MG).
- Consider T1D also in patients with MG with nonspecific symptoms such as weight loss.
- First case report of co-occurrence of MG and T1D in a prepubertal child from US.

Clinical Relevance

This is first case report of co-occurrence of MG and T1D in a prepubertal child from United States. In contrast to the reports from Europe, our patient developed MG first and T1D later. Consider screening for T1D in patients with MG.

Table 1
Prior reports of children and adolescents with co-occurring type 1 diabetes mellitus and myasthenia gravis

Reference	Year	Country	Sex	Age at diagnosis of T1D (years)	Age at diagnosis of MG (years)	Antibody testing for T1D	Antibody testing for MG	Comments
3	1983	Germany	Male	12	12	NR	NR	Primary adrenal insufficiency diagnosed at 12 y.
4	1989	United Kingdom	Male	12	14	NR	+ anti-acetyl choline receptor	Systemic juvenile chronic arthritis diagnosed at 7 y.
2	2019	Turkey	Female	4	4	+ anti-GAD65 - anti-insulin - anti-islet cell	- anti-acetyl choline receptor - anti-muscle specific tyrosine kinase	Tissue transglutaminase IgA, anti-endomysial IgA, and anti-gliadin IgA positive. Tissue transglutaminase IgG and anti-gliadin IgG negative. No duodenal biopsy results reported.
5	2019	Japan	Female	15	10	+ anti-GAD65	+ anti-acetyl choline receptor	Graves' disease diagnosed at 35 y.
6	2020	United Kingdom	NR	6.5	7	NR	- anti-acetyl choline receptor - anti-muscle specific tyrosine kinase - anti-ganglioside	
This report	2022	United States	Female	11	4	+ anti-GAD65 - anti-insulin - anti-islet cell + anti-ZnT8	+ anti-acetyl choline receptor	Anti-tissue transglutaminase IgA negative. Anti-thyroglobulin and anti-thyroid peroxidase antibodies negative.

TID, type 1 diabetes mellitus; MG, myasthenia gravis; NR, not reported; + positive, - negative; GAD, Glutamic acid decarboxylase 65; ZnT8, zinc transporter 8.

Table 2
Laboratory parameters at type 1 diabetes mellitus diagnosis

Laboratory parameter	Result	Reference Range
pH	7.36	7.32–7.42
Serum glucose mg/dl	268	<200
Bicarbonate meq/L	17	22–32
β-hydroxy butyrate mmol/L (mg/dL)	3.48	0.02–0.27
Hemoglobin A1c %	14.9	4.3–5.6
Sodium mmol/L	133	133–143
Potassium mmol/L	3.8	3.4–4.7
Calcium mg/dl	9.5	8.5–10.5
Phosphorus mg/dl	3.4	3.3–6.2
Serum osmolality mOsm/kg	291	290–300
Urine analysis	3+ glucose, 2+ketones	
Anti - glutamic acid decarboxylase antibody IU/mL	113.5	<5
Anti - zinc transporter 8 antibody IU/mL	>500	<15
Anti - islet antigen 2 (IA-2) antibody IU/mL	<5.4	<7.4
Anti - insulin antibody IU/mL	<0.4	<0.4
TSH μIU/mL	1.67	0.35–5.5
Free T4 ng/dL	1.20	0.8–1.8
Anti - thyroid peroxidase antibody IU/mL	<28	<28
Anti - thyroglobulin antibody IU/mL	<15	<15
Immunoglobulin A (IgA) mg/dL	298	21–282
Tissue transglutaminase IgA IU/mL	2.3	<14.9

common in pre-pubertal presentations of MG.[2] Other autoimmune diseases, such as autoimmune thyroid disease and celiac disease, can be associated with T1D.[1] Likewise, MG has been associated with other autoimmune conditions such as systemic lupus erythematosus, autoimmune thyroid disease, and rheumatoid arthritis.[2] Human leukocyte antigen (HLA) alleles and/or non-HLA gene loci at the intersection of T1D and MG risk, may increase the risk of developing both T1D and MG.[1,5] For example, in a case series of 10 patients with T1D, autoimmune thyroid disease, and MG all were found to have the HLA DR9/DQ9 subtype.[5] Authors suggested that patients with ocular type MG with the HLA DR9/DQ9 subtype should be screened for the risk of developing T1D.[5] Screening for autoantibodies has both pros and cons. Early identification of children with presymptomatic Type 1 diabetes helps in educating caregivers regarding symptoms of hyperglycemia which can decrease the risk of diabetic ketoacidosis (DKA) at diagnosis. It can also have a positive influence on glycemic control leading to reduced acute and chronic complications.[8] However, knowledge of positive auto-antibody status may cause increased anxiety among patients and caregivers specifically because of the unpredictability of disease onset and lack of therapeutic interventions for those younger than 8 years of age or who have stage 1 diabetes (ie, positive auto-antibodies with normoglycemia).[9] Immune modulator teplizumab is approved for use in children 8 years and older with stage 2 diabetes (ie, positive auto-antibodies and dysglycemia) to delay the development of T1D.[10] In large population studies, polymorphisms of the CTSL2 gene encoding cysteine protease cathepsin V, which is involved in antigen presentation in cortical thymic epithelial cells, have been associated with both T1D and early onset MG defined as onset before 40 years of age.[1] HLA typing or CTSL2 gene polymorphisms reports were not available for our patient.

The co-existence of MG and T1D is rare in both pediatric patient groups. A large retrospective study of 260 patients aged 3 to 23 years diagnosed with T1D observed MG in only one patient (0.4%) over the 14 year study period.[1] In a study of 149 children with MG diagnosed before 17 years of age and followed for a median of 17 years, T1D was reported in 3 patients (2.01%).[11] Further information on the age at diagnosis of MG and T1D was not available to verify if they were diagnosed < 18 years of age. We identified 5 case reports in the literature describing co-occurrence T1D and MG in children below 18 years: 4 from Europe and 1 from Asia (Table 1).[2-6] Significant autoimmune disease heterogeneity exists by race and by geographic area.[12] All the prior reported patients, except one from Japan, were diagnosed with T1D prior to or concurrently with MG.[2-6] In contrast, our patient was first diagnosed with MG and subsequently diagnosed with T1D 7 years later.

Conclusions

This is a rare case of co-occurrence of seropositive MG and T1D in a prepubertal child from the United States. History of autoimmune disease increases the risk for other autoimmune diseases. Consider screening for T1D in patients with MG and offering treatment to those above 8 years and older with stage 2 T1D to delay its onset. Along with other causes, T1D should also be considered when patients with MG present with nonspecific symptoms such as fatigue and weight loss.

Disclosure

The authors have no multiplicity of interest to disclose.

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