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JUVENILE DIABETES MELLITUS IN A CROSSBRED DOG. CASE REPORT

DIABETUL ZAHARAT JUVENIL LA UN CĂȚEL. RAPORTARE DE CAZ

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ABSTRACT | REZUMAT

A 5-month-old male crossbred dog weighing 2.3 kg was presented with polyphagia, polyuria, polydipsia, dehydration, thin skin, growth retardation and plantigrade stance. The stools were steatorrheic indicating exocrine pancreatic disfunction. High values of alkaline phosphatase and alanine aminotransferase were indicative of lipidosis and pancreas diseases. The dog exhibited hypoproteinemia associated with hypoalbuminemia, indicating most likely that protein malabsorption caused probably by exocrine pancreatic dysfunction. Severe hypocalcemia (1.39 mmol/L) with swollen joints suggests rickets. The diagnosis of diabetes mellitus was based on the presence of clinical signs (polyuria, polydipsia, polyphagia, weight loss) and evidence of fasting hyperglycemia and glycosuria. The very low serum total thyroxine (0.84 µg/dL) pointed to thyroid dysfunction. Blood insulin was very low 1.9µU/mL indicating an absolute deficiency of insulin secretion. Small values of insulin-like growth factor I concentration (6.10 nmol/L) and serum insulin, explain the growth retardation observed in our dog with juvenile diabetes mellitus. The aim of therapy (insulin, pancreatic enzymes and levothyroxine) is to eliminate the symptoms of diabetes mellitus and prevent short-term complications, thereby enabling the animal to have a good quality of life.

Keywords: diabetes, insulin, exocrine pancreatic insufficiency, canine

Un cățel metis, mascul de 5 luni cântărind 2,3 kg a fost prezentat la clinică cu polifagie, poliurie, polidipsie, deshidratare, piele subțire, retard de creștere și membre cu poziție plantigradă. Materiile fecale erau steatoreice indicând disfuncție pancreatică exocrină. Valorile ridicate ale fosfatazei alcaline și alanin aminotransferazei indică lipidoza și afecțiuni ale pancreasului. Câinele prezenta hipoproteinemie asociată cu hipoalbuminemia, indicând cel mai probabil malabsorbția proteinelor provocată de disfuncția pancreatică exocrină. Hipocalcemia severă (1,39 mmol / l) dar și mărirea în volum a articulațiilor sugerează rahitismul. Diagnosticul diabetului zaharat s-a bazat pe semnele clinice (poliurie, polidipsie, polifagie, pierdere în greutate) și analizele de laborator, hiperglicemie și glicozuriei. Valoarea mica a tiroxinei totale serice (0,84 µg / dl) a indicat disfuncție tiroidiană. Insulina din sânge a fost foarte scăzută de 1,9 pU/ml marcând o deficiență absolută a secreției de insulină. Valorile foarte mici ale concentrației de insulin-like growth factor I (6,10 nmol/l) și ale insulinei serice explică întârzierea creșterii și dezvoltării observată la pacientul cu diabet zaharat juvenil. Scopurile terapiei (insulină, enzime pancreatice și levothyroxină) sunt de a elimina simptomele diabetului zaharat și de a preveni complicațiile pe termen scurt, permițând astfel animalului să aibă o bună calitate a vieții.

Cuvinte cheie: diabet, insulină, insuficiență pancreatică exocrină, câine

Diabetes mellitus (DM) is a common endocrinopathy of adult dogs but less than 1.5% of diabetic dogs have juvenile diabetes (5). All reported cases of juvenile DM in animals have been similar to human type I or insulin dependent DM. Diabetic puppies present the classic clinical signs of polyuria, polydipsia, polyphagia, weight loss, blindness (caused by cataract formation), dehydration and muscle wasting.

Emaciated diabetic juveniles often have concurrent underlying disorders such as exocrine pancreatic insufficiency (EPI). In puppies, exocrine pancreatic insufficiency may present with signs similar to those of DM (polyphagia and weight loss) but with the additional signs of severe diarrhoea or steatorrhea resulting from impaired fat digestion. Clinical manifestations of EPI have rarely been reported in dogs less than 6 months old (16).

In this case report we describe the clinical and pathologic findings in a male crossbred dog with juvenile diabetes mellitus accompanied by exocrine pancreatic insufficiency.

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MATERIALS AND METHODS

A 5-months old male crossbred dog weighing 2.3 kg was presented with polyphagia, polyuria, polydipsia, growth retardation and plantigrade stance.

The owner said that the dog has a good appetite, but his growth is very slow compared with that of his normal littermates. He reported that the dog frequently produced voluminous soft, pale and oily stools. The puppy was vaccinated and dewormed. Physical examination and complete blood and urine analysis were performed. Endocrine tests were made to investigate the potential mechanisms involved in growth retardation as well as to rule out other endocrine disorders that cause growth retardation. The dog was examined radiographically (bones) and by ultrasound.

Complete blood counts were made using the Scil Vet ABC Hematology Analyzer (Scil Animal Care Company, USA). Routine blood biochemistry was made by spectrophotometry method using the Accent 200 Chemistry Analyzer (Cormay, Switzerland). Hormonal analyses were made by chemiluminescence (IGF, insulin, TSH and TT4) and respectively electrochemiluminescence (ECLIA) for cortisol and ACTH.

RESULTS AND DISCUSSIONS

Clinical examination

Puppies are often presented to the veterinarian for delayed growth. The 5-months dog presented to our clinic was weighing 2.3 kg while his brother weighed about 10 kg. The puppy had small stature but the same dimensions as the adult animal (Fig. 1). Causes of inadequate growth can be divided into two categories: intrinsic defects of growing tissues (genetic and chromosomal abnormalities) and abnormalities in the environment of growing tissues (nutritional, metabolic, environmental and endocrine) (5).

Fig. 1. Crossbred dog, male, weighing 2.3 kg, 5-months old

A dietary history could reveal inadequate quantity and/or quality of feeding. Our dog had a good appetite and the food was adapted quantitatively and qualitatively to his age.

A physical examination showed that the dog was emaciated with mild dehydration, thin skin, thinning haircoat, polyphagia, polyuria, polydipsia steatorrhea and plantigrade stance (Fig. 2, 3, 4).

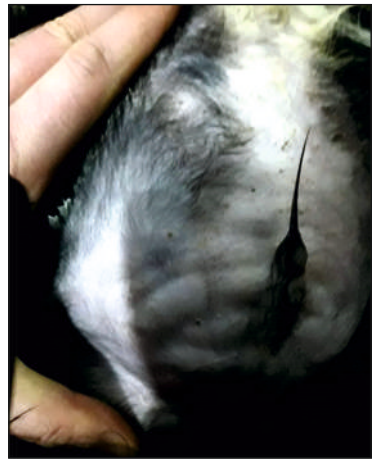

Fig. 2. Thin skin, intestines can be seen through the skin

Fig. 3. Steatorrhea in a dog

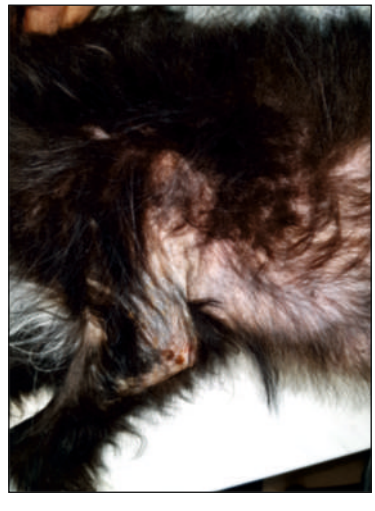

Fig. 4. Thinning haircoat in a dog

Table 1

Complete blood count in the juvenile dog

Parameter	Results		Range of Normal Values
	Day 1	Day 150	
RBC (x10^6/μL)	3.4	5.92	4.95-7.87
Hgb (g/dL)	8.2	12.5	11.9-18.9
PCV (%)	27	39	35-57
MCV (fL)	78.9	66	66-77
MCH (pg)	24	21.1	21-26.2
MCHC (g/dL)	30.4	32.1	32-36.3
Platelets (x10^3/μL)	325	591	211-621
WBC (x10^3/μL)	12.9	13.1	5-14.1
Lymphocytes (%)	25.6	11.5	8-21
Lymphocytes (x10^3/μL)	3.30	1.5	0.4-2.9
Monocytes (%)	10.4	6.3	2-10
Monocytes (x10^3/μL)	1.34	0.8	0.1-1.4
Neutrophils segmented (%)	52		58-85
Neutrophils segmented (x10^3/μL)	6.71		2.9-12
Neutrophils band (%)	6.4		0-3
Neutrophils band (x10^3/μL)	0.82		0-0.45
Eosinophils (%)	5.6		0-9
Eosinophils (x10^3/μL)	0.72		0-1.3
Basophils (%)	0		0-1
Basophils (x10^3/μL)	0		0-0.14

The menace response was present in both eyes. Dental eruption was relatively normal, considering the poor physical condition. Delayed dental eruption is characteristic of hypothyroid puppies. Congenital hypothyroidism is characterized by disproportionate dwarfism, central and peripheral nervous system abnormalities, mental deficiency, haircoat abnormalities including retention of the puppy haircoat and thinning haircoat (5). Our dog had subnormal stature (not true dwarfism) and proportionate as we find in juvenile diabetes mellitus. No problems were detected to the heart or lungs.

Laboratory analysis

In the first day of examination, the complete blood count showed hypochromic anaemia (Table 1). The serum biochemical analyses revealed the following: hyperglycemia (450 mg/dL), hypercholesterolemia (9.5 mmol/L), hypertriglyceridemia (4.2 mmol/L), hypoproteinemia (4.8 g/dL) with hypoalbuminemia (21.6 g/L) and elevated values of alkaline phosphatase (441 U/L), AST (76 U/L), and ALT 296 (U/L) (Table 2). High values of alkaline phosphatase and ALT indicate lipidosis and pancreas diseases. This puppy with severe hypocalcaemia (1.39 mmol/L) had also swollen joints which indicates rickets.

We analysed total bilirubin before (0.03 mg/dL) and after meals (0.01 mg/dL) and the results were within normal limits which indicate that the dog had no congenital portosystemic shunting. At abdominal ultrasound we observed hyperechoic liver (Fig 5).

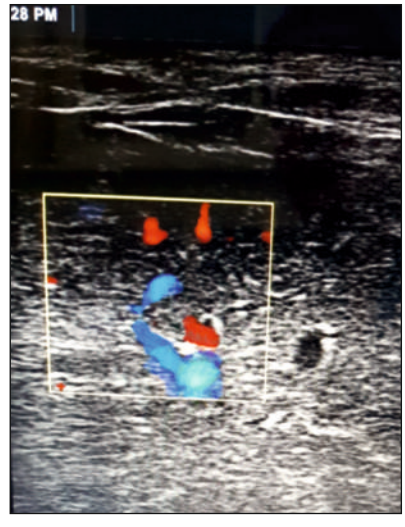

Fig. 5. Hyperechoic liver

In the present case, the dog also exhibited hypoproteinemia associated with hypoalbuminemia, indicating most likely that protein malabsorption caused probably by exocrine pancreatic dysfunction. Pancreatic enzymes were in normal limits but the stools were steatorrheic indicating also exocrine pancreatic dysfunction. Metabolic disorders such as congenital portosystemic shunting, exocrine pancreatic insufficiency, congenital heart disease and chronic renal failure

Table 2

Biochemical blood analyses in the juvenile dog

Parameter	Results			Range of Normal Values
	Day 1	Day 60	Day 150	
Amylase	245 U/L	973.2 U/L	750.2 U/L	226-1063 U/L
Total bilirubin	0,03 mg/dL before meals 0.01 mg/dL 2h after meals	-	-	0-0.3 mg/dL
Calcium	**1.39 mmol/L**	-	9.2 mg/dL	2.3-2.9 mmol/L 9.1-11.7 mg/dL
Alkaline phosphatase	**441 U/L**	**175 U/L**	**124 U/L**	1-114 U/L
GGT	6 U/L	6 U/L	-	1-9.7 U/L
Potassium	**5.7 mmol/L**	-	4.7 mmol/L	3.9-5.1 mmol/L
PO4	**8.8 mg/dL** 2.84 mmol/L	-	5.0 mg/dL	2.9-5.3 mg/dL 0.9-1.7 mmol/L
Total protein	**4.8 g/dL**	5.51 g/dL	6.2 g/dL	5.4-7.5 g/dL
Albumin	**21.6 g/L**	23.6 g/L	26 g/L	23-31 g/L
TGO (AST)	**76 U/L**	53 U/L	35 U/L	13-15 U/L
TGP (ALT)	**296 U/L**	32 U/L	-	10-109 U/L
Urea	**37.3 mg/dL** 6.2 mmol/L	-	-	7-28 mg/dL 2.9-10 mmol/L
Creatinine	0.57 mg/dL	0.9 mg/dL	-	0.5-1.7 mg/dL
Cholesterol	**9.5 mmol/L**			3.5-7.0 mmol/L
Triglycerides	**4.2 mmol/L**			0.2-1.3 mmol/L

can cause growth retardation. A complete urinalysis revealed a specific gravity of 1.033, bilirubin 1 mg/dL, leucocytes 15/µL, proteins 15 mg/dL, very high glucosuria (27.75 mmol/*L*), but not ketonuria.

A diagnosis of diabetes mellitus is based on the presence of clinical signs (polyuria, polydipsia, polyphagia, weight loss) and evidence of fasting hyperglycemia (>200 mg/dL) and glycosuria (4, 11).

There are four major types of diabetes. DM type 1 is also called insulin-dependent diabetes, is an absolute deficiency of insulin secretion due to T-cell mediated autoimmune destruction of the β-cells. DM type 2: is characterized by two defects: insulin resistance and β-cell dysfunction. Both are usually present at the time of diagnosis. It has genetic basis and is promoted by obesity, physical inactivity, certain drugs, and high glucose levels. The third category of diabetes (other specific types) refers to diabetes that develops in association with diseases or factors other than defined as type 1 or type 2. Diabetes can develop secondary to disorders of the exocrine pancreas (pancreatitis, pancreatic carcinoma), hypersecretion of counterregulatory hormones (hypersomatotropism, hypercortisolism, hyperthyroidism), and administration of glucocorticoids or progestins. The fourth category, in human gestational diabetes, has little importance in dogs and cats, but the diabetes associated with diestrus in dogs can be considered its equivalent.

The possible causes of canine juvenile DM are suggested to include congenital β-cell hypoplasia / abiotrophy, viral infection and/or autoimmunity (8). Viral disease (canine distemper) has been implicated in the pathogenesis of canine juvenile diabetes mellitus (5). The result at rapid test for canine distemper virus was negative in our dog.

Puppies with diabetes mellitus may present similar signs to those of exocrine pancreatic insufficiency (EPI). Canine EPI is a disease characterized by inadequate production of digestive enzymes from pancreatic acinar cells and it is diagnosed based on clinical signs and a decrease in the circulating trypsin-like immunoreactivity (TLI) concentration (12, 15).

The additional signs compared with DM, are severe diarrhea or steatorrhea resulting from impaired fat digestion. Our dog presented steatorrhea. Clinical manifestations of EPI have rarely been reported in dogs less than 6 months old (9, 16).

In the present case, the insulin-like growth factor I (IGF-I) concentration was very low (6.10 nmol/L). Normal serum IGF-1 concentration in German shepherd puppies are 345±50 ng/mL. This is much higher than the normal concentration in adult dogs. The mean IGF-1 concentrations for pituitary dwarf German shepherd dogs are 11±2 ng/mL (3).

Table 3

Endocrine analyses in the puppy

Parameter	Results		Range of Normal Values
	Day 1	Day 150	
IGF-I	**6.10nmol/L 46.90 ng/mL**	-	33.7-51.7nmol/L
Insulin	**1.9µU/mL**	-	9-32 µU/mL
Basal cortisol	0.67 µg/dL 18.5 nmol/L	-	13.7-165.5nmol/L
Cortisol at 90 min post Synachten®	8.50 µg/dL 234.5 nmol/L	-	200-550 nmol/L
TSH canin	**0.21 ng/mL**	0.45 ng/mL	<0.5ng/mL
TT4 canin	**0.84 µg/dL 10.81 nmol/L**	2.82 µg/dL 36.29 nmol/	1.3-2.9µg/dL 16.7-37.3nmol
Endogenous ACTH	10.2pmol/L	-	2.2-15.4pmol/L

IGF-I: Insulin-like growth factor I; TT_4: Total thyroxine, cTSH: Canine thyroid-stimulating hormone; ACTH: Adrenocorticotropic hormone.

Blood insulin was very low 1.9 µU/mL (normal limits 9-32 µU/mL), indicating an absolute deficiency of insulin secretion. Because both insulin deficiency and nutritional deprivation caused by DM can alter the growth hormone-insulin-like growth factor axis, which leads to decreased IGF-I synthesis, growth retardation can be observed in dogs with juvenile onset DM (2, 7).

Congenital hypothyroidism exhibit haircoat abnormalities including retention of the puppy hair coat and thinning haircoat. Clinicopathologic features of congenital hypothyroidism include hypercholesterolemia, mild anaemia and hypercalcemia (the result of decreased renal clearance and increased gastrointestinal absorption of calcium). Serum total thyroxine (TT4) of 2 µg/dL which is normal for an adult dog, is low for a 6-week-old puppy pointing thyroid dysfunction. Our dog had much lower the TT4 (0.84 µg/dL) which indicates hypothiroidism (Table 3).

Analyzing endogenous canine TSH (thyroid-stimulating hormone) allows us to discriminate primary congenital hypothyroidism from secondary hypothyroidism (TSH deficiency). Puppies with primary hypothyroidism (thyroid dysgenesis, dyshormonogenesis) have elevated endogenous TSH concentrations, whereas puppies with TSH deficiency have subnormal endogenous TSH concentrations. Our dog had normal TSH concentration which indicates a hypothiroidism secondary to chronic non thyroidal disease. Another explanation could be the primary hypothyroidism with false negative result. In this case the prognosis for the treatment is excellent if thyroid supplementation occurs before 6 months of age. After that, neurologic and skeletal damage may become irreversible. Thyroid hormones are crucial for growth and development of all body tissues and particularly the skeleton (13). Radiological examination did not reveal skeletal delayed maturation or epiphyseal dysgenesis, specific in congenital hypothyroidism (Fig. 6).

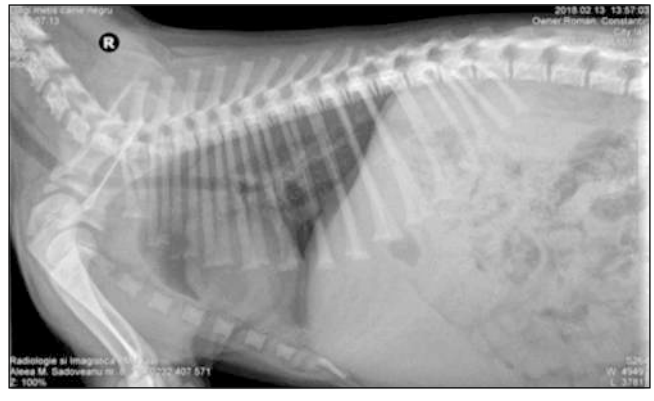

Fig. 6. Radiographic image of the thorax of the puppy

Polyuria and polydipsia also occur in primary hypocorticism, a primary adrenal insufficiency (Addison disease). Our puppy had a very low serum cortisol (0.67 µg/dL). For diagnosis we performed the Synacthen test. This is based on the measurement of serum cortisol before and after an injection of synthetic ACTH (also known as tetracosactrin). If the serum cortisol increases more than 550 nmol/L, 90 minutes after Synacthen® administration (0.125mg IM), it indicates the presence of the Cushing disease.

If serum cortisol decreases more than 200 nmol/L, 90 minutes after Synacthen® administration, it indicates the Addison disease.

Hypoadrenocorticism and DM may cause hindlimb paresis in addition to signs of metabolic disease. Diabetic cats and dogs may have a plantigrade stance. Control of metabolic disease commonly results in resolution of neurological dysfunction (11, 13).

Our puppy had a normal answer (values of cortisol 234.5 nmol/L) after Synacthen® administration. By analysing the serum ACTH of our puppy, we observe a normal value (10.2pmol/L) which does not confirm either Addison or Cushing disease.

The clinical manifestations and laboratory findings indicated that the dog had suffered from juvenile DM type1, and that exocrine pancreatic insufficiency and hypothyroidism might occur simultaneously. Concurrent DM and EPI may be due to simultaneous damage of the endocrine and exocrine pancreatic tissue.

Treatment of juvenile DM

It requires insulin therapy. The insulin was administrated subcutaneously. In the first day of treatment we used a human fast acting insulin Actrapid® to set the dose at which the dog responds by lowering blood sugar. Initially, the dog glycaemia was 454 mg/dL. Two hours after the first dose of insulin (0.5U/kg) the blood glucose decreased (413 mg/dL) but it was still higher than the reference range (76-119 mg/dL). Initial insulin therapy should be conservative followed by progressive increases in insulin dosage based on resolution of clinical signs, urine glucose monitoring and serial blood curves (Fig. 7).

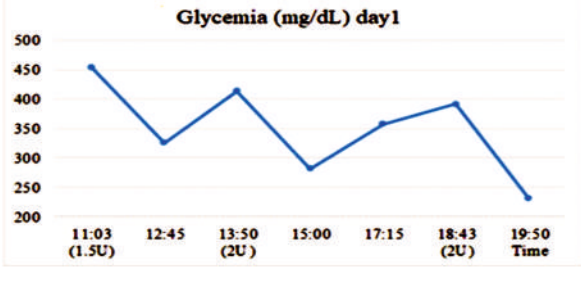

Fig. 7. Glycemia of the puppy in the first day of treatment with Actrapid® insulin

A glucose curve is required to differentiate between adequate insulin therapy and excessive therapy (hypoglycemic shock). We administrated a second dose of insulin but with 0.5 U higher than initial dose. One hour after the second dose (2 U) the blood glucose was 280 mg/dL. Three hours after the second dose, glycemia increased at 360 mg/dL. Four and a half hours after the second dose, glycemia was higher (390 mg/dL) and we administrated a third dose (2 U). One hour later the glycemia was 230 mg/dL. We fed the dog and injected the insulin at the same time.

The second day of treatment we administered Mixtard30® (containing both fast-acting (30%) and long-acting (isophane), 2 U subcutaneously twice a day (morning and evening). Next days we started to increase the insulin dose because the puppy had very high blood sugar oscillating until 400-580 mg/dL with moments of hypoglycaemia (Fig. 8). The glycemia was analysed with the same device, twice a day (morning and evening) before eating. After 2 weeks we changed the mixt insulin with long-acting insulin Lantus® (glargine) 2 U/kg twice a day. During the next weeks, under Lantus®, glycemia variated between 180-270 mg/dL. The dose of insulin was adjusted without exceeding 15 U/animal twice a day.

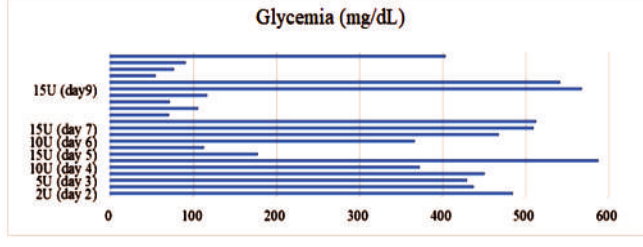

Fig. 8. Glycemia of the puppy with Mixtard30® insulin treatment

The treatment was completed with levothyroxine supplementation, (22 µg/kg per day, orally) to reverse the dermatologic and skeletal consequences of TSH deficiency during next 5 months. The puppy also received pancreatic enzymes Pancreazim® (dicalcium phosphate - 270 mg; protease - 30 mg; cellulase - 30 mg; alpha amylase - 15 mg; lactase - 15 mg; lipase - 15 mg) one pill/10 kg twice a day. After two weeks, the stools were normal, the puppy starting to gain weight suggesting a need to continue with a minimum effective maintenance dose of Pancreazim® per feeding for the rest of the dog life. Our puppy also received minerals and vitamins supplementation for two months to correct the rickets.

The aim of therapy was to eliminate the symptoms of juvenile diabetes mellitus type 1 and prevent short-term complications (hypoglycaemia and ketoacidosis), thereby enabling the animal to have a good quality of life.

The owner was instructed to administrate insulin (twice a day) and to monitor the effects by nothing

changes in appetite, attitude, body condition, polydipsia, polyuria, blood and urine glucose. High urine glucose readings associated with uncontrolled clinical signs, such as polyuria and polydipsia indicate that the insulin dose may be inadequate (5). Consistently negative readings on urine glucose may indicate that insulin dosage is either adequate or excessive.

Ideally glucosuria (<250-500 mg/dL) without ketonuria should be detected. In case of hypoglycaemia (<70 mg/dL) manifested with muscle spasms, lack of coordination of voluntary movements, loss of consciousness and shaking, the owner has to give the dog a teaspoon of sugar or honey.

Other indication for the owner were: feeding the dog three to four times daily with high quality protein, physical activity, and water consumption should be maintained within normal limits (10).

After 5 months of treatment the hematological and biochemical analyses were in normal limits. The puppy was given to another owner. After that, the puppy changed several times the owners. Because the treatment was uncompleted, often not given, the dog made cataract at both eyes. Cataract formation is a common complication in adult dogs with DM but its development in young dogs has rarely been reported (1, 6). The last owner did not consent to medical treatment of the dog and ultimately requested euthanasia.

CONCLUSIONS

The clinical manifestations and laboratory findings indicated that the dog had suffered from juvenile DM type 1, and that exocrine pancreatic insufficiency and hypothyroidism might occur simultaneously. Small values of insulin-like growth factor I concentration (6.10 nmol/L) and serum insulin, explain the growth retardation observed in our dog with juvenile diabetes mellitus. The aim of therapy is to eliminate the symptoms of diabetes mellitus and exocrine pancreatic insufficiency, and prevent short-term complications, thereby enabling the animal to have a good quality of life.

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