***Case Report***

# An Exceptional Triple Endocrinopathic Disorder; Schmidt's Syndrome in a Dog

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## Abstract

Polyglandular deficiency syndromes result from multiple endocrine failures and describe a combination of two or more organ-specific autoimmune disorders. Endocrine disorders may sometimes be deceptive, as a diagnosis of one failure may lead to a false satisfaction of the case, despite the resistance to treatment. The present case describes the Schmidt syndrome of a twelve-year-old, intact female mixed breed dog previously diagnosed with hypoadrenocorticism and inadequate response to treatment. Hypothyroidism and diabetes mellitus were diagnosed with a positive Antinuclear Antibody test. The treatment was initiated, resulting in clinical improvement with the absence of lethargy and seizures in a couple of days, and metabolic values returned to normal limits in two weeks. This is the first case of Schmidt syndrome (Polyglandular Adenopathy type 2) with triple endocrinopathy in a dog presenting immune intervention. We underline that the comorbid endocrinopathies with probable immune etiology must be considered in canine patients with suboptimal response to treatment for hypothyroidism or hypoadrenocorticism.

**Keywords:** Comorbid, Endocrinopathy, Hypothyroidism, Polyglandular Adenopathy

## Introduction

Polyglandular deficiency syndromes result from multiple endocrine end-organ failures and are characterized by the association of two or more organ-specific autoimmune disorders. (Schmidt, 1926) The polyglandular adenopathy (PGA) syndromes are classified into two main types: PGA type I and PGA type II. (Betterle et al., 2004)" Schmidt's Syndrome" is the combination of autoimmune adrenal insufficiency (Addison's disease) with autoimmune hypothyroidism and type 1 diabetes mellitus (PGA Type II). (Blois, 2011) Since Addison's disease and chronic lymphocytic thyroiditis were first reported in two patients by Schmidt in 1926, the presence of autoimmune Addison's disease and autoimmune thyroid disease is known as Schmidt's Syndrome (Gupta and Nagri, 2012; Cartwright et al., 2016). Schmidt's Syndrome is a sporadic autoimmune disorder and difficult to diagnose because the symptoms depend on the gland which gets involved first. In humans; the prevalence of Schmidt's Syndrome is 1.4-2.0 per 100,000 population (Gupta and Nagri, 2012). Polyglandular autoimmune endocrinopathies are not common in dogs (Adissu et al., 2010) though only a few cases of double-endocrinopathies were reported (Kooistra et al., 1995; Adissu et al., 2010; Blois et al., 2011) and two case reports with documented immune intervention (Pikula et al., 2007; Cartwright et al., 2016). This is the first case of canine polyglandular endocrinopathy including hypoadrenocorticism, hypothyroidism together with diabetes Mellitus in the presence of antinuclear antibodies.

**Case Presentation**

A twelve-years-old, intact female mixed breed dog referred with severe loss of appetite and intermittent episodic seizures. She was previously diagnosed with hypoadrenocorticism (ACTH stimulation test) and was under treatment with a very low dose of dexamethasone (0,01 mg/kg) every other day for two years, without any satisfactory results and the complaints (exhaustion, anorexia, frequent seizure episodes) continued as expected with this dosage. The referral's primary blood analysis revealed normocytic, normochromic anemia, severe hypoglycemia, low T4 value, and normal TSH measurements (Table 1).

**Table 1:** Serum biochemical analyse esults

| Test | Day 0 | Day 14 |
|---|---|---|
| TP (g/L) | 67 | 64 |
| ALB (g/L) | 35 | 38 |
| ALP (µkat/L) | 19.057 | 1.139 |
| GLU (mg/dL) | 30 | 120 |
| TBIL (mg/dL) | 0.4 | 0.2 |
| TCHO ( mg/dL) | 203 | 190 |
| GGT (µkat/L) | 0.316 | 0.133 |
| ALT (µkat/L) | 0.714 | 0.68 |
| Ca (mg/dL) | 12.4 | 10.2 |
| CRE (mg/dL) | 0.5 | 0.56 |
| BUN ( mg/dL) | 10.3 | 19.2 |
| TT4 (ug/dL) | 0.6 | 1.6 |
| TSH ( ng/mL) | 0.87 | 0.31 |
| Cortisol (ug/dL) | 0.9 | 3 |

TP: Total Protein, ALB: Albümin, ALP: Alkaline Phosphatase ,GLU: Glucose, TBIL: Total Bilirubin, TCHO: Total Cholesterol, GGT: Gamma-Glutamyl Transferase, ALT: Alanine Aminotransferase, Ca: Calsium, CRE: Creatinine, BUN: Blood Urea Nitrogen ,TT4: Total T4, TSH: Thyroid-Stimulating Hormone

ACTH stimulation test (Feldman and Nelson, 2004) was repeated with pre (27.2 nmol/L), and post cortisol (27.9 nmol/L) results demonstrating hypoadrenocorticism. Anti Nuclear Antigen (ANA) test was also positive (speckled), revealing immune intervention. The triple endocrinopathy indicated Schmidt's Syndrome. Treatment started with supportive therapy and 22 mcg/kg Levothyroxine (LEVOTIRON®100 mcg tablet, Abdi İbrahim, Turkey) two times a day, 2 mg/kg prednisolone (PREDNOL® 16 mg tablet, Mustafa Nevzat, Turkey) once a day, together with glargine insulin 0.5 IU/kg (LANTUS SOLOSTAR® 100 u/ml BID, Sanofi Aventis, Germany). Clinical improvement with the absence of lethargy and seizures was achieved in a couple of days, and metabolic values turned back to normal limits in two weeks. The dog had a stable clinical and metabolic manner up to date for eight months due to monthly periodic visits and minimal therapeutic adjustments.

**Discussion**

A polyglandular endocrinopathy of a combination of autoimmune adrenal insufficiency (Addison's disease) with autoimmune hypothyroidism and type 1 diabetes mellitus (IDDM) was described and named by the researchers name, Schmidt in 1926 (Schmidt, 1926). It is a part of autoimmune polyendocrine syndrome type II or polyglandular autoimmune syndrome type II (Betterle et al., 2004).

Glandular endocrinopathies are common in dogs, but polyglandular endocrinopathies are substantially rare (Adissu et al., 2010). The first report on a canine case of polyglandular endocrinopathy was published on a boxer dog with primary hypothyroidism and the primary adrenocortical deficiency (Addison Disease) (Kooistra et al., 1995), and the author expressed the identity of the canine condition with type II polyglandular autoimmunity or Schmidt's Syndrome in humans. Even so, they did not search for the immune intervention with a triple endocrinopathy including diabetes mellitus, hyperadrenocorticism (Cushing disease), and hypothyroidism in a six-years-old mix breed, spayed female without any immune parameters (Kooistra et al. 1995, Hess and Ward 1998). This case was not fitting type II polyglandular autoimmunity or Schmidt's Syndrome due to the presence of Cushing's disease. The following report of canine polyendocrinopathy was published after nine years in 2007 (Pikula et al., 2007). They described a 6-year-old female dog with polyglandular failure syndrome, including hypothyroidism and hypoadrenocorticism. Indirect immunofluorescence revealed the presence of circulating autoantibodies against the thyroid gland. This was the first case of canine autoimmune polyendocrinopathy in literature, although the immune intervention was detected only for the thyroid gland. In 2010, published a case of a 4.5-year-old spayed female Great Pyrenees with hypothyroidism and hypoadrenocorticism with a slightly enlarged pituitary gland and bilaterally atrophic adrenal and thyroid glands (Adissu et al., 2010). Interestingly, the dog did not respond to supplementation with prednisone and levothyroxine and was euthanized. Again, no autoimmune intervention was demonstrated in this paper.

Next year, a retrospective work was published on 35 dogs with more than one endocrine disorder in which 80% had two disorders, and the rest had three (Blois et al., 2011). Surprisingly, the most common endocrine disorders in this population of dogs were diabetes mellitus and hyperadrenocorticism, followed by hypoadrenocorticism and hypothyroidism. A mean of 14.5 months elapsed between diagnosis of the first and second endocrine disorders, whereas there was a mean of 31.1 months between diagnosis of the first and third endocrine disorders. In the present work, a triple endocrinopathy is mentioned, and two years were elapsed between the diagnosis of the first and the rest two endocrinopathies.

The only entire immune-mediated case of Schmidt (primary hypothyroidism and primary cortisol secondary hypoadrenocorticism) was reported in a three-year-old female Doberman pinscher (Cartwright et al., 2016). Clinical symptoms were generally similar, except for the azotemia, which was absent in our dog. Increased serum concentrations of thyroglobulin autoantibodies and 21-hydroxylase autoantibodies indicated an immune-mediated etiology in that case and clinical signs resolved following the introduction of levothyroxine and prednisolone similar to the present case.

A hallmark of systemic autoimmune disease is the high titer of circulating antinuclear antibodies (ANA), which is demonstrated by the indirect immunofluorescence (IIF) ANA test. (Hansson-Hamlin et al., 2012) A positive ANA test was generally associated with Systemic Lupus Erythematosus (SLE) in dogs. However, studies demonstrated that this was not a functional diagnostic test in dogs without any significant clinical or clinicopathologic abnormalities suggestive of SLE. There was a good chance that the results of the ANA assay would be positive and that the dog would be found to have the immune-mediated disease if at least two significant signs were evident (Bremer et al., 2015). In ANA-positive dogs, different immunodiffusion subgroups could be correlated to different ANA subgroups (Hansson and Karlsson-Parra, 1999). Antinuclear antibodies include a broad autoantibody group targeting different antigens in the cell membrane (Hansson et al., 1996, Smee et al., 2007). Because ANA positivity may be detected in healthy individuals or under varying clinical conditions, it is suggested that ANA assays are likely to be positive and compatible with the immune-mediated disease if at least two major clinical signs were evident, as in the present case (Adissu et al. 2010). Different patterns of ANA positivity, based on IIF-ANA and immunodiffusion results, may be associated with different systemic autoimmune diseases in dogs, and precipitating antibodies are strictly associated with a speckled IIF-ANA staining pattern concordant with our analysis.

This is the first case of Schmidt syndrome (PGA2) with triple endocrinopathy in a dog presenting immune intervention. Also, immune status is displayed by the ANA test, which we recommend especially for practice regarding availability and rapid results. In conclusion, polyglandular endocrinopathies with probable immune etiology must be considered in canine patients with suboptimal response to treatment for hypothyroidism or hypoadrenocorticism.

**References**

**Adissu, H.A., Hamel-Jolette, A., Foster, R.A. (2010).** Lymphocytic adenohypophysitis and adrenalitis in a dog with adrenal and thyroid atrophy. Vet Pathol 47(6):1082-1085.

**Betterle, C., Lazzarotto, F., Presotto, F. (2004).** Autoimmune polyglandular syndrome Type 2: the tip of an iceberg?Clin Exp Immunol 137(2):225–233.

**Blois, S.L., Dickie, E., Kruth, S.A., Allen, D.G. (2011).** Multiple endocrine diseases in dogs: 35 cases (1996-2009). J Am Vet Med Assoc 238(12):1616-1621

**Bremer, H.D., Lattwein, E., Renneker, S., Lilliehöök I., Rönnelid J., Hansson-Hamlin H. (2015).** Identification of specific antinuclear antibodies in dogs using a line immunoassay and enzyme-linked immunosorbent assay. Vet Immunol Immunopathol 168(3-4):233-41.

**Cartwright, J.A., Stone, J., Rick, M., Dunning, M.D. (2016).** Polyglandular endocrinopathy type II (Schmidt's syndrome) in a Dobermann pinscher. J Small Anim Pract 57(9):491-494.

**Feldman, E.C., Nelson, R.W. (2004).** Canine and Feline Endocrinology and Reproduction. 3rd ed. St. Louis, USA: WB Saunders, 394-439.

**Gupta, A.N., Nagri, S.K. (2012).** Schmidt's syndrome - Case report. Australas Med J 5(6):292–295.

**Hansson-Hamlin, H., Lilliehöök, I., Trowald-Wigh, G. (2012).** Subgroups of canine antinuclear antibodies in relation to laboratory and clinical findings in immune-mediated disease. Vet Clin Pathol 35(4):397-404.

**Hansson, H., Karlsson-Parra, A. (1999).** Canine antinuclear antibodies: comparison of immunofluorescence staining patterns and precipitin reactivity.

Acta Vet Scand 40(3):205-212.

**Hansson, H., Trowald-Wigh, G., Karlsson-Parra, A. (1996).** Detection of antinuclear antibodies by indirect immunofluorescence in dog sera: comparison of rat liver tissue and human epithelial-2 cells as antigenic substrate. J Vet Intern Med 10(4):199-203.

**Hess, R.S., Ward, C.R. (1998).** Diabetes mellitus, hyperadrenocorticism, and hypothyroidism in a dog. J Am Anim Hosp Assoc 34(3):204-207

**Kooistra, H.S., Rijnberk, A., Van den Ingh, T.S. (1995).** Polyglandular deficiency syndrome in a boxer dog: thyroid hormone and glucocorticoid deficiency. Vet Q 17(2):59-63.

**Pikula, J., Pikulova, J., Bandouchova, H., Hajkova, P., and Faldyna, M. (2007).** Schmidt ' s Syndrome in a Dog : A Case Report (9):419–22.

**Schmidt, M.B. (1926).** Eine biglandulare Erkrankung (Nebennieren und Schild- drüse) bei Morbus Addisonii. Verh Dtsch Ges Pathol 21:212–221.

**Smee, N.M., Harkin, K.R., Wilkerson, M.J. (2007).** Measurement of serum antinuclear antibody titer in dogs with and without systemic lupus erythematosus: 120 cases (1997-2005). J Am Vet Med Assoc 230(8):1180-3.