Adrenocortical hypofunction. Polyglandular autoimmune syndromes

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Adrenocortical hypofunction

Definition

Cases of adrenal insufficiency can be divided into two general categories:

1. Primary inability of the adrenals to elaborate sufficient quantities of hormone

2. Secondary failure due to inadequate ACTH formation or release

Adrenal insufficiency

Classification

- Primary
- Secondary

Primary adrenal insufficiency = Addison's Disease

- Autoimmun - sporadic, Autoimmun polyendocrine sy type I, II
- Infections – tuberculosis, fungal, viral

- Metastatic tumor
- Infiltrations - amyloid, haemochromatosis

- Intra-adrenal haemorrhage - Waterhouse – Friedrichsen sy
- Adrenoleukodystrophies

- Congenital adrenal hyperplasia
- ACTH resistance syndromes

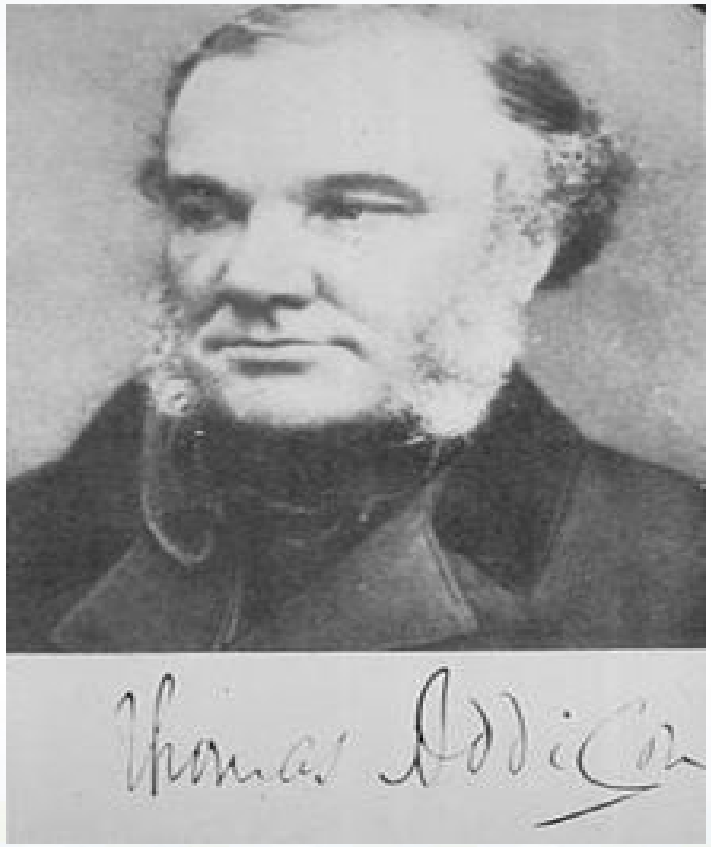
- Bilateral adrenalectomy

Adrenocortical hypofunction
Addison’s disease

The original description of Addison’s disease:

„ general languor and debility, feebleness of the heart’s action, irritability of the stomach, and a peculiar change of the color of the skin”

Thomas Addison (1793-1860)



- Adrenocortical deficiency and pernicious anaemia
- (1849): ‘Anaemia—disease of the suprarenal capsules in which the disease is not distinctly separated from a new form of anaemia’
- In Addison's day tuberculosis was found at autopsy in 70-90% of cases.

Autoimmune adrenalitis

- 70% of all cases
- Atrophic glands, but medulla is intact
- Autoantibodies
- 50% of patients have an associated autoimmun disease (APS)

Infections

- A very common cause as well

- Tuberculosis: extraadrenal disease is also evident, both the cortex and medulla are affected
- Fungal infections (cryptococcosis, histoplasmosis), cytomegalovirus
- **AIDS** – 10 % of patients show subnormal response to Synacthen test

- Some drugs for treatment may precipitate the adrenal insufficiency (ketokonazol: inhibits cortisol synthesis, rifampicin: increases cortizol metabolism)

Acquired primary adrenal insufficiency

- Adrenal metastases: breast, lung-rarely cause adrenal insufficiency
- Necrosis of the glands – should be considered in any severely sick patient (infection, trauma, coagulopathy)
- Waterhouse – Friedrichsen sy associated with meningococci

Waterhouse- Friedrichsen syndrome

- bleeding into the gland
- Severe infection with meningococcus bacteria

- It can be caused by procoagulants

- Other causes: low platelet count, primary antiphospholipid syndrome, renal vein thrombosis, steroid use

Inherited primary adrenal insufficiency

- Adrenal hypoplasia congenita – X-linked disorder (combined with primary and central hypogonadotropic hypogonadism)
- **Adrenoleukodystrophy**
- Familial glucocorticoid deficiency – AR cause, it ususally manifests in childhood
- Triple A syndrome (adrenal insuff, achalasia, alacrima)

Adrenoleukodystrophy

- X-linked inherited disorder
- Prevalence 1:20000
- Disease of the very-long chain fatty acid metabolism
- Progressive neurological symptoms of demyelinisation

Secondary causes

- Glucocorticoid therapy
- Hypopituitarism
- Selective removal of ACTH secreting pit. adenoma
- Pituitary tumors, and pituitary surgery, craniopharyngeomas, pituitary apoplexy, pituitary irradiation
- Granulomatous disease
- Postpartum pituitary infarction (Sheehan’s sy)
- Secondary tumor deposits
- Isolated ACTH deficiency, Multiple pituitary hormon deficiencies

Hypadrenalism during critical illness

- Even in individuals with previously intact HPA axis
- Functional adrenal insufficiency
- Hypadrenia is transient, no structural lesion
- Uncertain etiology
- Inability to mount an adequate and appropriate cortisol response to stress on intensive care units
- Increases the risk of death during acute illness
- Treatment with relatively high doses of hydrocortizon, or with methylprednisolon in septic shock, and early phase of acute respiratory distress is recommended

Clinical features

Addison's disease - epidemiology

- Prevalence: 93-140/1 million
- Incidence: 4.7 – 6.2/ 1 million/year
- Young adults
- Woman are affected (more frequent)

Symptoms

90% of glands must be destroyed to manifest clinically - high functional reserve

- Weakness, tiredness, fatigue - gradually 99%
- Pigmentation of skin 98%
- Anorexia, weight loss 97%
- Gastrointestinal symptoms: nausea, vomiting,(90%) constipation, abdominal pain (34%), diarrhoea (20%) – it can cause Addison's crisis
- Salt craving – muscle spasm (22%)
- Postural dizziness, syncope (16%)
- Vitiligo (9%)

Signs and laboratory findings

Signs

- Weight loss
- Hyperpigmentation
- Hypotension (80/50 Hgmm or less)
- Vitiligo
- Auricular calcification
- Sexual dysfunction

Laboratory findings

- Electrolyte disturbancies
  - hyponatremia
  - hyperkalemia
  - hypercalcaemia
- Azotaemia
- Anaemia
- Eosinophilia

Addison’s disease

Addison’s crisis

- Medical emergency
- Dehidration, hypotension or shock out of proportion to severity of current illness
- Nausea and vomiting, with a history of anorexia
- Acute abdomen
- Unexplained hypoglycaemia
- Unexplained fever

Investigation

- Routine biochemical profile
- Mineralocorticoid status
- Assessing adequacy of function of the HPA axis
- Testing the HPA axis during critical illness
- Other tests

Assessing adequacy of function of the HPA axis

- Basal plasma cortisol and UFC levels are often in the low-normal range

- A basal cortisol value greater than 14.5 ug/dl (400 nmol/l) indicates an intact HPA axis

Diagnosis

- **ACTH stimulation**

  250 ug Synacthen iv – cortisol response 30 min after.

  Cortisol level should exceed 495 nmol/l (= 18 ug/dl) – assay dependent

If the response is abnormal, measure aldosteron levels (in secondary aldosterone increasement will be normal>5 ng/dl)

Differentialdiagnosis

- Because symptoms are common, and unspecific, early diagnosis is difficult
- Racial pigmentation can be a problem
- Hyperpigmentation is usually absent when adrenal destruction is rapid, as in bilateral adrenal haemorrhage
- Hyperpigmentation can also occur with other diseases together

Treatment

- Treatment of acute adrenal insufficiency
- Long-term replacement therapy

Treatment of acute adrenal insufficiency

- Treatment should not be delayed while waiting for definitive proof of diagnosis
- Plasma electrolyte, glucose and appropriate samples for ACTH and cortisol should be taken before CS therapy
- Then: 2-3 l 0.9% NaCl solution, or 50 g/l (5%) dextrose in 0.9% saline solution as soon as possible
- Monitor fluid overload by measuring central venous pressure
- Iv 100 mg hydrocortison and every 6 hr

Long term treatment

- Specific hormone replacement
  (it should correct both glucocorticoid
  and mineralocorticoid deficits)

- **Thorough education about the disease!**

- Cortizol 20-30 mg/d (it should be taken with meals)
- Two-third of the dose is taken in the morning, one third is taken late afternoon
- Optimizing therapy only by clinical symptoms
- Fludrocortizone 0.05-0.1 mg/d, liberal salt intake

Special therapeutic problems

- Intercurrent illness – fever: double dose
- Severe illness 75-150 mg/d (when oral administration is not possible, parenteral routes)
- Fludrocortison dose should be increased and add salt to the normal diet during period of exacting exercise with sweating, diarrhoea, extremely hot weather
- Major surgery (the day of surgery it will mimic the output of cortisol in normal individuals undergoing prolonged major stress)

DHEA supplementation?

- DHEA: controversial
- It can improve the patient’s mood and well-being
- Indicated for treatment of postmenopausal woman
- Is this the drug for eternal youth?
- 25-50 mg/die

Secondary adrenal insufficiency

- HPA axis failure
  - deficiency of glucocorticoids and adrenal androgens
  - mineralocorticoids are unaffected

- 1 cause = chronic exogenous glucocorticoid
  - suppresses diurnal CRH/ACTH release
  - both time and dose related (short course, and daily dose of prednisolone 5 mg or less)
  - reversible (recovery may take up to a year)

Summary

„ Unexplained hyponatremia and hyperkalemia in the setting of hypotension unresponsive for catecholamin and fluid administration….

…..should receive 100 mg hyrocortisone intravenously”

Case presentation

Sz. V. 29 years old female

- History: appendectomy, nasal plastical surgery
- No drugs taken
- Smoking: 2-3 cigarettes/day
- Family:sister hypothyreosis, psoriasis
- Menses regular

- **Complaints:** since 1 year progressive tiredness, weakness mainly in evenings, brownish skin color

Results

- **Lab tests:** glu: 5 mmol/l, Na: 128 mmol/l, K: 5.8 mmol/l, CN: 9.1 mmol/l, kreat: 107 umol/l, CRP: 1.90 mg/l

- Kortizol: 1.55 ug/dl (=42.8 nmol/l) (Ref: 220-690); ACTH: 1991 pg/ml (Ref: 7.2-63); DHEAS: 12 ug/dl (Ref: 130-330)

- Antibody against the adrenal cortex: strongly poz

Addison’s disease

Gluco – and mineralocorticoid supplementation

20-5-10 mg hydrocortizon (Cortef)
2x0.1 mg fludrocortizon (Astonin H)

Adrenal CT

- Both adrenals were atrophic, gracile, hardly identified. In the region of the left adrenal can only be a stout vessel visualized

Follow-up, provision of care

- 2 weeks after beginning the therapy: she is well, she can work
- **Lab tests:** glu: 4.3 mmol/l, Na: 136 mmol/l, K: 4.3 mmol/l, Ca: 2.28 mmol/l
- IgA: 1.69 g/l (0.7-4.0), IgM. 1.68 g/l (0.4-2.3), IgG: 14.62 g/l (7-16)

Other screening tests

- PTH: 56 pg/ml
- TSH: 10.199 mU/l (0.35-4.9)
- T4: 12.01 pmol/l (9.0-23.2)
- aTPO: 1508.5 U/ml (0.0-63)
- TRAK: 0.3 IU/l negative

- Immun: GADA – negative

- EMA: strongly pos, aTTg IgA: 84 U (0-20)
- ANA and every other antibodies are negative

Diagnosis: Autoimmun Polyglandular syndrome (APS) type II

Natural history of autoimmun disorders

- Stages beginning with genetic susceptibility (genes of immunregulation – AIRE)
- Followed by triggering of autoimmunity – environmental factors (iodine, viruses)
- Active autoimmunity preceding clinical manifestations
- Overt disease

AIRE (autoimmune regulator)

- AIRE gene is localized on chromosome 21q22.3
- highest concentration in thymus
- but also found in lymph nodes, spleen, and fetal liver

Model of the pathogenesis of autoimmunity in polyendocrine disorders

Introduction

- The term “polyendocrine” itself is a misname
- not all patients have multiple endocrine disorders
- many have nonendocrine autoimmune diseases

N Engl J Med 2004;350:2068-79

APS – I.

- Epidemiology 1:9000 – 1:200000
- Female:male = 1 : 2.4
- Imunregulatory gene defect (AIRE gen – 21 q)
- Candidiasis: because of a T-cell defect
- Genetic: AR, monogenic, inherited disease, doesn’t accompanied to HLA antigens
- Mutations of AIRE gene

APS – I.

- = APECED (Autoimmune polyendocrinopathy, Candidiasis, Ectodermal Dystrophy) = Whitaker-sy
- It begins in childhood
- Minor symptoms can present prior to the main symptomps in the early 20th years

(hepatitis, keratoconjunctivitis, periodic rashes with fever, chronic diarrhea, celiac disease, severe obstipation, alopecia, or vitiligo)

Introduction

- APECED appears to occur worldwide

- common only in Iranian Jews, Sardinians, and Finns
  - Iranian Jews (1:9,000)
  - Sardinians (1:14,000)
  - Finns (1:25,000)

Clinical manifestation

- **Whitaker's triad** of symptoms—

  1. chronic mucocutaneous candidal infections (CMC)
  2. hypoparathyroidism
  3. adrenocortical failure (Addison's disease)

  is pathognomonic for APECED

- CMC is the first sign (75–93%) followed by
- Hypoparathyroidism, (peak age 4-5 yr) then by
- Addison's disease (also in childhood)

Ann. N.Y. Acad. Sci. 1246 (2011) 77–91

*Hans D. Ochs,et al.,*Primary Immunodeficiency Diseases: A Molecular and Genetic 2nd edition

Candidiasis

- mucocutaneous candidiasis : oral, ungual, esophagial and vaginal mucosa and nails

  - Oral candidiasis
  - Candidal esophagitis →esophageal stricture or squamous cell carcinoma
  - Perianal candidal eczema
  - intestinal mucosal candidiasis
  - Infection of skin of the hands ,face and nails
  - Candidal vulvovaginitis (after puberty)

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Endocrine manifestation

- Apart from hypoparathyroidism and Addison's disease,
  - hypergonadotropic hypogonadism
  - type 1 diabetes
  - autoimmune thyroid diseases
  - pituitary defects
  - gastric parietal cell atrophy

→ autoimmune origin

often associated with a specific set of organ-specific autoantibodies

Ann. N.Y. Acad. Sci. 1246 (2011) 77–91

Management

- Hormone replacement : endocrinopathies
  - insulin in type 1 diabetes mellitus
  - calcium and vitamin D in hypoparathyroidism
  - thyroid hormone in hypothyroidism

Nat. Rev. Endocrinol. 7, 25–33 (2011)

Nat. Rev. Endocrinol. 6, 270–277 (2010)

Management

- Mucocutaneous candidiasis must be treated aggressively and monitored for recurrence

  – antifungal agents should be started at presentation
  – anywhere along GI tract
  – if left untreated → squamous cell carcinoma of the oral cavity or esophagus

Nat. Rev. Endocrinol. 7, 25–33 (2011)

Nat. Rev. Endocrinol. 6, 270–277 (2010)

APS – II. (Schmidt sy)

- Addison’s disease + T1DM (52%) or autoimmun thyroid disease (70%)
- Minor criterias: vitiligo, atrophic gastritis, hypergonadotropic hypogonadism, autoimmun hepatitis, alopecia, anaemia perniciosa, myasthenia gravis, hypophysitis, celiac disease
- 2-3 fold common in woman
- AD inheritance
- Role of HLA antigenes (HLA DR3/DR4) és IR genes

APS – I.

- Early beginning (childhood)
- Mutation of AIRE gene
- No HLA association
- Immundeficiency
- Mucocutan candidiasis

APS – II.

- Later beginning (adults)
- No mutation of AIRE gene
- Association with HLA DR3/DR4
- No immundeficiency
- No mucocutaneous candidiasis

APS – III.

- Autoimmun thyroid disease(TAD = thyreoid associated disease: Hashimoto, Basedow, endokrin orbitopathy)

  + 28% other autoimmun disease:

  Sjögren, coeliakia, SLE, myasthenia

- Many autoimmun disorders are mild, subclinical form

- 7-8% in the population

APS – III. Classification

APS – 3A	APS – 3B	APS – 3C	APS – 3D
endocrin	gastrointestinal	Hematology/skin/nervous system	Systemic - collagen
T1DM	Autoimmun gastritis	Vitiligo	MCTD
Hirata-disease	Anaemia perniciosa, IBD	Alopecia areata	RA
Hypophysitis	Autoimmun hepatitis	ITP	SLE
Addison’s disease	PBC	Myasthenia gravis	Sjögren
Hypoparathyreosis		Sclerosis mpx	Vasculitis

Differential diagnosis

- Turner-sy (autoimmun thyreoiditis 30% and other endocrinopathies)

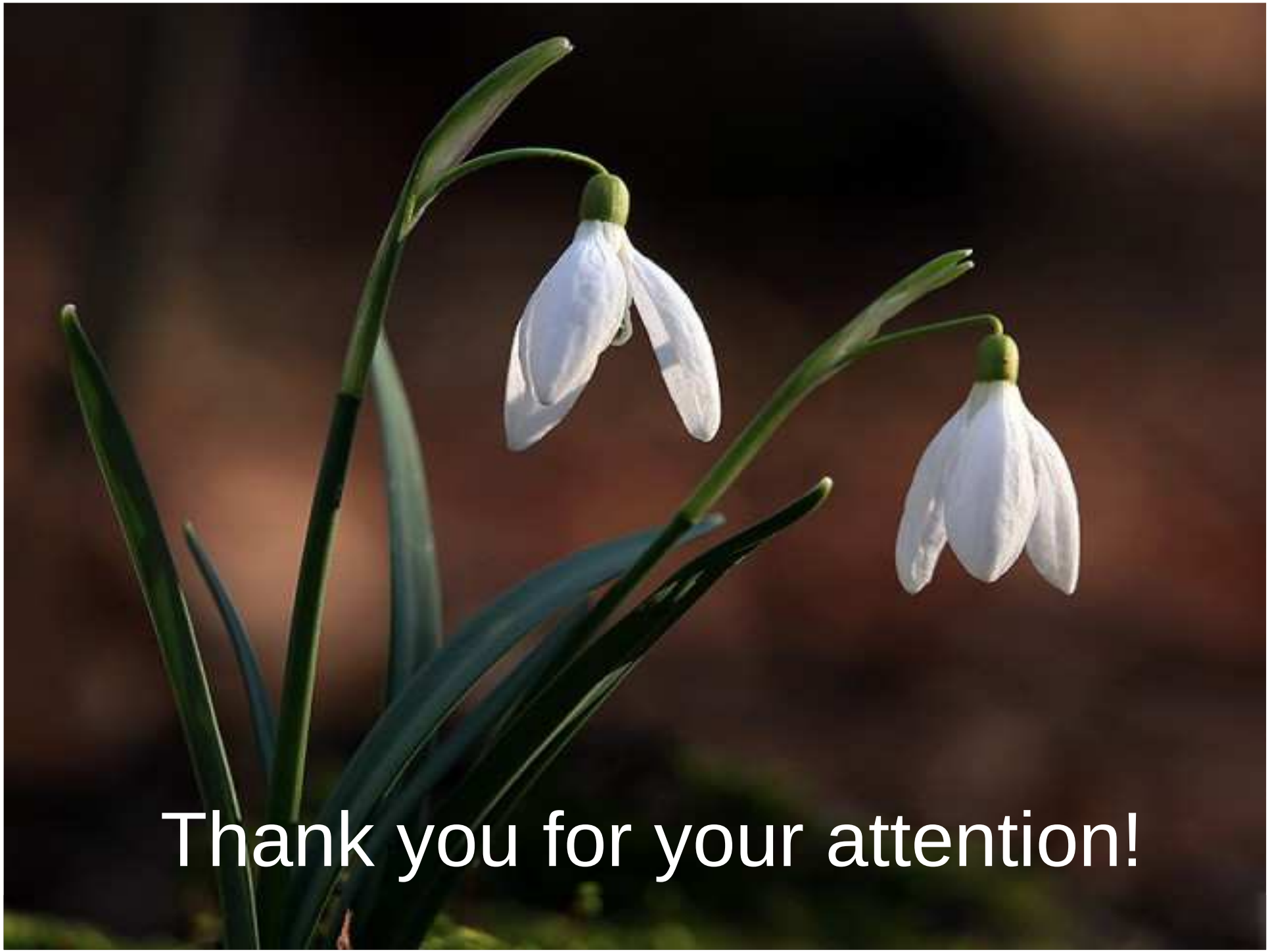
- Kearns - Syre sy : main complaint is myopathy, but hypoparathyreosis, primary hypogonadism, T1DM, hypopituitarism can also occur

- Wolfram sy – begins in childhood

  (DM, DI, atrophy of the nervus opticus, deafness)

- With thorough treatment patients can usually cope with the disease and their life expectancy is only slightly decreased

- oral squamous cell carcinoma or a sudden onset of the disease by hypocalcemic or Addisonian crisis or acute hepatitis can sometimes be of a fulminant nature


Thank you for your attention!