International Journal of Homoeopathic Sciences

E-ISSN: 2616-4493
P-ISSN: 2616-4485
www.homoeopathicjournal.com
IJHS 2021; 5(4): 16-19
Received: 21-05-2021
Accepted: 12-07-2021

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Cushing's syndrome- a systematic review with homoeopathic management

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DOI: https://doi.org/10.33545/26164485.2021.v5.i4a.449

Abstract
Distinct clinical syndromes are produced when excessive amounts of the adrenocortical hormones are secreted. Excess production of glucocorticoids occurs in Cushing' syndrome.
Homoeopathy is known to control the not only the Cushing syndrome butalso useful in all other endocrinal disorders. In case of Cushing syndrome the Homoeopathic medicines work by reducing the symptoms.

Keywords: Plasma glucocorticoid, cortisol excess, adrenocorticotropic hormone, moon face, growth retardation, homoeopathy

1. Introduction
Cushing's syndrome comprises the symptoms and signs associated with prolonged exposure to inappropriately elevated levels of free plasma glucocorticoid. The elevated corticosteroid levels that may be found in severely depressed patients but which appear to be appropriate to the condition and also the increased total glucocorticoid levels found when there is an increase in circulating cortisol-binding globulin. The use of the term glucocorticoid in the definition covers both endogenous and exogenous excess [1, 2].
Cushing's syndrome is generally considered a rare disease. It occurs with an incidence of 1–2 per 100,000 population per year. it is debated whether mild cortisol excess may be more prevalent among patients with several features of Cushing's such as centripetal obesity, type 2 diabetes, and osteoporotic vertebral Column fractures, are relatively nonspecific and common. In majority of patients, Cushing's syndrome is caused by an ACTH-producing corticotrope adenoma of the pituitary, as initially described by Harvey Cushing in 1912. Cushing's disease more frequently affects women, with the exception of prepubertal cases, where it is more common in boys [3].
When severe hypercortisolism presents, its signs and symptoms are unmistakable. The commonest sort of signs and symptoms of Cushing's syndrome are common within the general population (e.g., hypertension and weight gain) and not all are present in every patient. Apart from the classical features of glucocorticoid excess, like proximal muscle weakness and wide purple striae, patients may present with the associated comorbidities that are caused by hypercortisolism. These clinical features include disorder, thromboembolic disease, psychiatric and cognitive deficits, and infections. Considering this results it must consider Cushing's syndrome as a cause, and endocrinologists should look for and treat these comorbidities [4].

2. Aetiology
Cushing's syndrome is caused by increased activation of glucocorticoid receptors. By far the foremost common cause is iatrogenic, thanks to prolonged administration of synthetic glucocorticoids like prednisolone. Non-iatrogenic Cushing's syndrome is rare and is often a 'spot diagnosis' made by an astute clinician [5].

2.1 Endogenous causes
2.1.1. ACTH - dependent
- Pituitary tumour (Cushing's disease)
- Excessive CRH secretion
- Ectopic - ACTH secretion by non-endocrine tumours (bronchogenic, carcinoid, thymus, pancreas, ovary and thyroid)

2.1.2. Non-ACTH dependent
Adrenal pathology
2.2 Exogenous causes.

- Glucocorticoid administration [6].
- Iatrogenic (e.g. prednisolone)
- Adrenal adenoma
- Adrenal carcinoma [7].

3. Clinical features

- The typical patient with Cushing's syndrome is a middle-aged plethoric woman with truncal obesity and hypertension.
- Other prominent symptoms are weakness, fatigue, emotional disturbances, moonfaced, and osteoporosis.
- The obesity of Cushing's is classically truncal in nature with sparing of limbs.
- There is accentuation of normal fat over the upper part of the back, giving rise to typical "buffalo hump". The neck is thick and short.
- The supraclavicular fat pads are enlarged.
- Patients may have proximal myopathy; muscle wasting may be prominent.
- Weakness may be aggravated by associated hypokalaemia.
- Increased hepatic gluconeogenesis and insulin resistance result in an abnormal glucose tolerance test.
- There is demineralisation of bones leading to pathologic fractures and vertebral collapse.
- Low back pain is a common presenting feature [8].

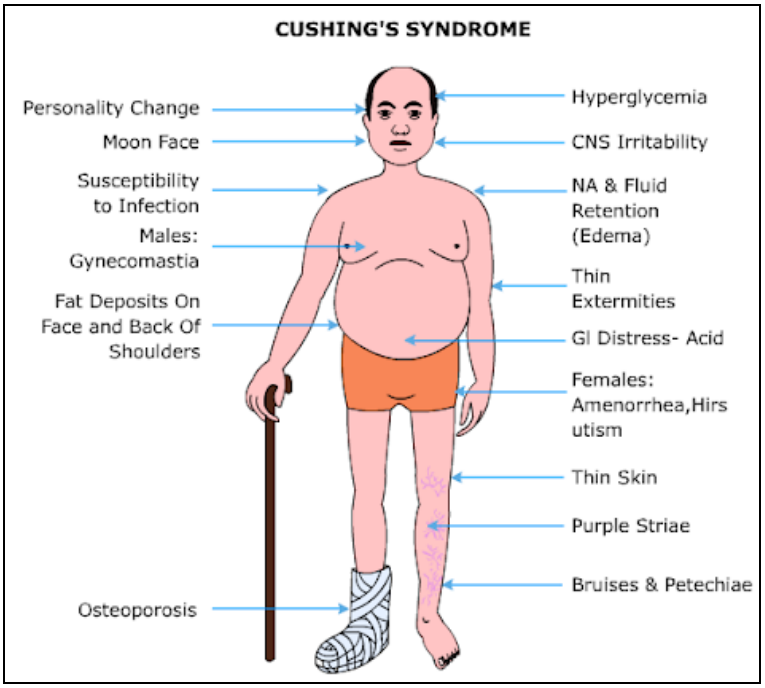

Fig 1: Symptoms of Cushing syndrome.

- Young patients show signs of growth retardation.
- There may be gastric ulcer.
- Patients exhibit emotional changes, ranging from irritability to severe depression, confusion and frank psychosis.
- In women, acne, hirsutism, oligomenorrhoea and amenorrhoea are common presentations. Moderate hypertension is almost always present.
- High levels of cortisol are associated with decrease in lymphocyte and eosinophil counts.
- The incidence of intercurrent infections and pulmonary tuberculosis is high. Besides, patients are prone to cutaneous fungal infections. Polycythaemia is also a common feature.
- There is delayed wound healing and easy bruisability of the skin. The skin is atrophic, and there is loss of subcutaneous fat, and underlying blood vessels are seen.
- Numerous purplish striae (more than 1 cm wide) are seen over the trunk and abdomen [9].

4. Differential diagnosis

This can be extremely difficult since all causes may result in clinically identical Cushing's syndrome. The classical ectopic ACTH syndrome is distinguished by a brief history, pigmentation and weight loss, unprovoked hypokalaemia, clinical or latent diabetes and plasma ACTH levels above 200 ng/L, but many ectopic tumours are benign and mimic pituitary disease closely both clinically and biochemically. Severe hirsutism/virilization suggests an adrenal tumour [10].

5. Investigations to confirm the diagnosis include:
Clinical Examination

In the absence of a good clinical presentation, biochemical tests are needed to establish the diagnosis. Cushing's syndrome screening is most likely to be positive in the presence of signs that are most typical of glucocorticoid excess, such as abnormal fat distribution in the supraclavicular and temporal fossae, proximal muscle weakness, wide (>1 cm) purple striae, and new irritability, decreased cognition, and decreased short-term memory. Testing is indicated when clinical features have progressed over time. For example, oligomenorrhea is more suggestive of Cushing's syndrome if a woman had previously regular menses [11].

- **48-hour low-dose dexamethasone test**. Normal individuals suppress plasma cortisol to < 50 nmol/L. Patients with Cushing's syndrome fail to show complete suppression of plasma cortisol levels (although levels may fall substantially in a few cases). This test is highly sensitive (> 97%). The overnight dexamethasone test is slightly simpler, but has a higher false-positive rate.

- **24-hour urinary free cortisol measurements.** This is simple, but less reliable - repeatedly normal values (corrected for body mass) render the diagnosis most unlikely, but some patients with Cushing's have normal values on some collections (approximately 10%).

- **Circadian rhythm.** After 48 hours in hospital, cortisol samples are taken at 0900 h and 2400 h (without warning the patient). Normal subjects show a pronounced circadian variation those with Cushing's syndrome have high midnight cortisol levels (> 100 nmol/L), though the 0900 h value may be normal [11, 12].

Other tests. There are frequent exceptions to the classic responses to diagnostic tests in Cushing's syndrome. If any clinical suspicion of Cushing's remains after preliminary tests then specialist investigations are still indicated, these may include insulin stress test, desmopressin stimulation test and CRH tests [10, 13].

6. Treatment

- Trans-sphenoidal resection of ACTH producing pituitary tumours
- Unilateral adenoma: Adrenalectomy
- Bilateral tumours: Bilateral adrenalectomy Postoperatively cortisol should be given [14]

- **Pituitary radiotherapy**

Persistent hypercortisolemia after transsphenoidal surgery due to residual tumour can be treated with radiotherapy. Adjunctive medical control of hyper cortisolemia may be needed while awaiting the effects of radiotherapy. Conventional fractionated radiotherapy is very effective, but its effects may be delayed up to 10 years, and it can be associated with long-term hypopituitarism [15, 16].

7. Complications of Cushing Syndrome

- Heart attack and stroke
- Blood clots in the legs and lungs
- Infections
- Bone loss and fractures
- High blood pressure
- Unhealthy cholesterol levels
- Depression or other mood changes [17]
- Memory loss or trouble concentrating
- Insulin resistance and prediabetes
- Type 2 diabetes [18]

8. Homoeopathic Management For Cushing Syndrome

8.1 Repertorial representation-

8.1.1 Complete repertory by Roger van zandvoort

- Generalities > Cushing's disease (1): 1 mark = Chlorpromazinum [19]

8.1.2 Murphy repertory [20] Clinical - CUSHING'S, disease chlorpr.

8.1.3 Synthesis repertory: GENERALS - CUSHING's syndrome -cortico. cortiso [21].

8.2. Homoeopathic Therapeutics

Quercus Robur

- It is useful in dropsy, reduced mental responsiveness, puffiness, cravings, ascites, breathlessness and varicose veins which can be seen in Cushing's disease.
- Sick unto death" with ascites and dropsy of the legs. The urine at once increased, but the patient complained that each dose of the medicine caused constriction of the chest.
- Unable to state his own case. Flushed, much pain over the eyes and in both rib regions. Stooping caused great pain, < left hypochondrium.
- Nervous, depressed, glum, taciturn, easily moved to tears; not quite capable of stating his own case.
- Liver and spleen much enlarged. Nervous, depressed, glum, taciturn, easily moved to tears. Could not walk without support on account of his great giddiness.

Adrenalinum

- This is very good for adrenal balance.
- It is useful for Cushing's syndrome treatment caused by an over-productive adrenal gland as we normally see in ACTH-independent Cushing's syndrome [22]

Arsenicum Album

- This is very good for excessive thirst (usually due to diabetic complications);
- Face swollen, pale, yellow cachectic sunken cold and covered with sweat.
- Skin is raw and burning, swelling eruptions papular dry rough worse by cold and scratching.
- Pulse is more rapid in morning [23].
- Digestive upset including nausea, vomiting and stomach pains; skin problems like itching, burning, dry and easily irritated skin.
- All these symptoms can be seen in people suffering from Cushing's disease.

Pituitarum Posterium

- Very good for most people with Cushing's disease who have ACTH-dependent Cushing's syndrome.
- This is because it helps with problems in the pituitary glands.

Sulphur:

- This helps with pain (due to osteoporosis which is weakening of the bones seen in Cushing's syndrome),
- Frequent urination (can be seen in diabetic complications of Cushing's syndrome), skin problems and liver problems [22].
- Standing is the worst position.
- Dirty, filthy people prone to skin affections.
- Very forgetful, difficulty in thinking [23].

Chelidonium Majus

- Is useful in the liver, bile, and digestive issues in Cushing's syndrome.
- Constant pain under inferior angle of right scapula [24].
- Tongue coated thickly yellow, with red edges, showing imprint of teeth, large, flabby, with imprint of teeth.
- Desire for very hot drinks, unless almost boiling

stomach will not retain them.
- Periodic orbital neuralgia (right side), with excessive lachrymation; tears fairly gush out [25].

Hepar Sulphuris Calcareum
- Useful in skin problems, abdominal distention due to ascites or bloating, and liver problems.

Mercurius Solubilis
- Useful for digestive issues, jaundice, enlarged liver, vertigo, intense thirst, memory and thinking issues, and belching.
- The perspiration is offensive; it has a strong, sweetish, penetrating odor.
- Offensiveness runs all through; offensive urine, stool and sweat; the odors from the nose and mouth are offensive.
- When Mercurius is used in large doses and the patient is salivated he gives off these odors [25, 26]

Abbreviations: ACTH (Adrenocorticotropic Hormone), >(more than), <(less than), CRH (Corticotropin-releasing Hormone).

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