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Review Article

Cushing Syndrome: A Review and its Treatment by Emerging Molecule Osilodrostat

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Abstract

Cushing syndrome is mainly the Hypercortisolism state in our body which is due to many factors like inappropriate exposure of Glucocorticoids. It can be endogenous as well as exogenous depending upon the cause and responsible factors. Screening of Cushing syndrome includes procedures like UFC test, Low Dose DST, Low dose salivary cortisol levels. Diagnosis of the Syndrome involves the MRI of Pituitary gland, Overnight Dexamethasone test. Some of complications arising from this syndrome are excessive weight gain, Hypertension, Diabetes mellitus, decreased immune response, depression and Depression. Treatment of Cushing syndrome is done by various therapies like Pituitary surgery, adrenal surgery and medical treatment which involve use of various drugs for treatment. Osilodrostat has shown very impressive results in treatment of Cushing Syndrome as compared to other available options of drugs like Ketoconazole and Metyrapone. Further studies are to be done on Osilodrostat to conclude a perfect and permanent treatment of Cushing Syndrome.

Key words: cushing syndrome; hypercortisolism; glucocorticoids; diabetes mellitus; dexamethasone; ketoconazole; osilodrostat

Introduction

Cushing's syndrome is characterized by the excess levels of Cortisol in the body. Effect of cortisol can be seen on whole body tissues alone or at multiple sites in body. Excessive and inappropriate exposure of free circulating Glucocorticoids in the blood stream leads to the disease state called as Cushing Syndrome [1]. Complications in the Cushing syndrome include Hypertension, Metabolism related problems, some manifestations related to respiratory tract like asthma, Type –II Diabetes Mellitus, osteoporosis and rheumatoid arthritis [2]. Symptoms of Cushing syndrome include thinning of skin, body's slow response to healing of injuries, unexpected weight gain, some other symptoms like fatigue, weakness and acne. We can categorize the Cushing Syndrome into two types: Endogenous and exogenous. Treatment of Inflammatory, neoplastic and autoimmune disorders may lead to exogenous cause of Cushing Syndrome. Endogenous cause of Cushing Syndrome can be associated with patients having history of uncontrollable Diabetes mellitus and cardiovascular diseases like Hypertension [3]. Cushing Syndrome can be categorized as: Adrenocorticotrophic Hormone (ACTH) dependent and Adrenocorticotrophic (ACTH) - Independent[4]. 80-85 % cases account for the ACTH-dependent mechanism of Cushing Syndrome, whereas only 15-20 % cases contribute for the ACTH-Independent endogenous Cushing Syndrome [4]. Diagnosis of Cushing Syndrome includes mainly by 2 screening tests: Late night salivary cortisol test, 24- Hour cortisol free test or low dose Dexamethasone test [5]. Osilodrostat can be used as a promising therapy option for treating Cushing Syndrome. Its mechanism of action is by inhibiting the cortisol biosynthesis in the adrenal cortex [6].

Signs and symptoms:

Some signs and symptoms associated with the Cushing Disease are:

Weight gain can be seen in most of cases, (50%). Generally receptive distribution of fat, some conditions like Buffalo hump, moon face [7].

Cardiovascular abnormalities like Hypertension.

Purplish or purplish-red marks (grooves on skin) of Breast area, abdominal lower part, thighs.

Edema of lower limbs.

Impaired glucose metabolism that leads to disease like Type-II Diabetes, mellitus.

Bones related diseases like osteoporosis, poor blood supply to bones parts especially in femoral head area.

As a consequence of ACTH-MSH cross reactivity, hyper pigmentation of skin and mucus membrane occurs. This occurs mainly in high levels of ACTH.

Neurodisorders like Depression, loss of memory, emotional distress [8].

Decreased immune response and recurrent infections.

Screening tests for cushing syndrome:

The main purpose of screening tests is to check the increased level of cortisol in the body, Impaired ACTH negative feedback mechanism which in involved in Pituitary-Adrenal axis, loss of diurnal variation of ACTH and cortisol.

1. **First line screening tests:**

- **Urine free cortisol test/ 24 hours urinary free cortisol (ufc) [9]:**

This test is used to indicate or to evaluate the free or unbound cumulative amount of free cortisol which is circulating in 24 hours in the blood stream. Three samples are to be collected in the 24 hours to measure the cortisol levels both bound and unbound. If the results of all three collected samples are in normal value, same or nearby to eachother, it is the indication of normal renal functioning. Thus there are no signs and symptoms of Cushing disease. Glomerular filtration rate (GFR), urinary creatinine level is used to identify the indication of cortisol production. GFR below 30 ml/min is the indication of decreased urinary cortisol excretion however, the production of cortisol is normal. Measurement, separation of Glucocorticoids and cortisol metabolites can be done by High Performance Liquid Chromatography (HPLC) method. Immunoassay methods (RIA, immunometric assays) are used to measure urinary cortisol levels.

- **Low dose dexamethasone (1 mg) suppression test (dst) [10]:**

The purpose of this screening test is to identify the unsuppressed dexamethasone despite of the cause of disease. 1 mg dose of dexamethasone is to be given to the patient on time 23:00 to 24:00 PM. Serum cortisol level is to be determined by the next day morning between 8:00 to 9:00 AM. Value of serum cortisol is to be determined and compared with standard values. If serum Cortisol levels exceed 1.8 mg/dl (50nmol/L), it is an indication of positive diagnosis of Cushing syndrome. Cortisol suppression is not seen in patients suffering from depression or obesity.

- **Late night salivary cortisol test [11]:**

Cortisol concentrations reach maximum at midnight. Sample of patient was collected in late night 23:00 PM and evaluated for cortisol levels. It is a promising test for screening of Cushing disease.

1.Second line screening tets:

- **Midnight plasma cortisol test/ measurement of plasma cortisol circadian rhythm:**

There is an abnormal increase in the serum cortisol level of patients suffering from Cushing Syndrome accompanied by lacking of approximately normal value of heart rhythm. Patient cortisol levels at midnight greater than1.8 µg/ml indicate presence of Cushing Disease.

- **Low dose cst and combined dst-crh test [12]:**

In this test 0.5 mg of Dexamethasone is given to patient orally after every 6th hour. The serum sample is to be collected at morning time 9:00 AM till 48 hours. On the basis of Low dose CRH - DST test it can be stated that patients with Pseudo Cushing syndrome have less CRH release due to stress condition. In such patients a clear response to exogenous CRH stimulation after a specific dose of 0.5 mg of Dexamethasone is given. Plasma cortisol value greater than 1.4 µg/ dl indicate the presence of Cushing syndrome.

Diagnostic tests for cushing syndrome:

1.Magnetic resonance ivestigation (mri) of pituitary gland:

MRI is used to detect the presence or absence of pituitary adenomas. In radiological imaging, Macroadenomas can be seen, which indicates the presence of Cushing disease. Differentiation of normal pituitary tissues from pituitary adenomas can be done by MRI with contrast administration of 0.05 nmol/kg of Gadolinium [13].

2.Overnight dexamethasone test:

The purpose of this diagnostic test is to identify difference between ectopic Adrenocorticotrophic hormone secretion and Cushing syndrome. Procedure for this diagnostic involves the administration of 8mg of Dexamethasone at a single time at midnight around 23:00 PM or 2 mg after every 6 hours. Serum sample to be collected at morning 8:00 to 9:00 AM followed by identification of serum cortisol levels. Increase in the serum cortisol levels is the indication of ectopic source of ACTH, and low secretion indication of Confirmation of Cushing Syndrome [14].

Cause of cushing syndrome:

Etiology of Cushing's syndrome includes its two types: the endogenous and exogenous hypercortisolism. Most common cause of Cushing syndrome is exogenous type which is due to very long regular use of Glucocorticoids and it founds to be iatrogenic. Endogenous cause of Cushing syndrome can be categorized as ACTH Dependent and ACTH independent. In endogenous cause of Cushing syndrome there is an increase in the production of Cortisol by the Adrenal glands. Factors responsible for ACTH dependent endogenous Cushing syndrome are ACTH – secreting pituitary adenomas, ectopic ACTH secretion by neoplasm. Factors responsible for ACTH- independent Cushing syndrome are adrenal hyperplasia, adenoma, and carcinomas [15,16].

Treatment of cushing syndrome:

Treatment of Cushing syndrome includes three lines of treatment namely: First line of treatment, second line of treatment and third line of treatment. First line Treatment includes treatment algorithm and Pituitary surgery. Second line treatment includes Pituitary radiotherapy and Adrenal surgery. The third line or medical therapy includes various classes of medications for the treatment of Cushing Syndrome.

First line treatment:

1. **Treatment algorithm:** Treatment algorithm include the selective elimination of pituitary tumor (adenomectomy). It also includes removal of half pituitary gland (hemi – hypophysectomy) or nearly entire pituitary gland (total hypophysectomy) [17]. In past time Transcranial Surgery was used but its use is very limited in Cushing Syndrome now a days. A surgical approach to treat pituitary lesions in Cushing syndrome is known as transsphenoidal surgery. There may be cortisol deficiency after the pituitary surgery which is balanced by the glucocorticoid therapy till Hypothalamus pituitary adrenal axis fully recovers [18].
2. **Pituitary Surgery:** This treatment method mainly includes the elimination of pituitary tumor by the method known as Transsphenoidal surgery (TSS). TSS can be employed on patients mainly by the two methods: The microscopic and the endoscopic method. Microscopic method mainly includes the use of nasal speculum to examine the surface of sphenoid sinus and opening of sphenoid and sellar floor [19].

Second line treatment:

If there is increase or no change in the increased cortisol levels in the patient with Cushing syndrome, additional treatment is to be given to patient to minimize the risk of complications regarding hypercortisolism. Hypersecretion of Cortisol in the body even after surgery is due to the remaining hidden tumor in the gland in cavernous sinus, in an ectopic parasellar region. In such conditions, there may be some treatment methods which can be employed which include repeat pituitary surgery, pituitary radiotherapy and adrenal surgery. Repeat pituitary surgery is done in cases where the imaging proof of residual tumor is seen in patient. There may be sometimes multimodal approach can be used to achieve best outcome and satisfactory results with patient compliance [20,21].

- **Pituitary Radiotherapy:** Pituitary radiotherapy was used as first line treatment in the time of 1940s to the 1980s. Due to improvement and advancement in the technology, it has become a second line treatment in recent days. Pituitary radiotherapy is a promising method of treatment for the patients who refuse to surgery, and for invasive pituitary tumors [22]. There are two methods employed for the Pituitary radiotherapy: The conventional radiotherapy (CRT) and stereotactic radiotherapy (SRT).

In CRT method, the delivery of ionizing radiation is done to the pituitary gland, the purpose of this method is to control the hormone hypersecretion and to stop the growth of tumor. LINAC is used to generate the photons

and the CRT is given in multiple sessions according to the treatment schedule and need of patient. Dose of radiation generally ranges from 45-50 Gy at time. It can be higher or lower but maintaining a total dose of 1.8 to 3.0 Gy per fraction.

SRT method includes the delivery of ionizing radiations on the tumor surface directly to control the increased secretion and to diminish tumor growth. GK and LINAC SRS are used for this purpose which involves the delivery of focused radiation to the target in a single treatment [23].

- **Adrenal Surgery:** Adrenal surgery is an option of treatment for the patients with repeated unsuccessful pituitary surgery or fast requirement of controlling Cortisol levels due to presence of some serious health complications and diseases. Adrenal surgery can be can in two ways: Bilateral adrenalectomy and unilateral adrenalectomy. Bilateral surgery of adrenal gland involves the removal of both adrenal glands so as to decrease or to control the increased Cortisol levels. Unilateral adrenalectomy involves the mechanism of surgery by which only one adrenal gland is removed by surgery and other gland is kept for production of cortisol in the body endogenously [24,25].

3.Third line or Medical Treatment:

Medical treatment of Cushing syndrome includes the various classes of drugs as:

- Drugs which cause the suppression in the production of cortisol by inhibition of enzymes involved in steroid genesis, also called as adrenal -directed drugs. The drugs included in this class are Ketoconazole, Metyrapone, Aminoglutethimide, trilostane, Etomidate, Mitotane [26,27].
- Drugs responsible for the inhibition of cortisol production and tumor ACTH secretion known as pituitary directed drugs. Drugs in this category are Cyproheptadine, Valproic acid and Bromocriptine [28].
- Drugs used to block the activation of glucocorticoid receptor peripherally; however the adrenal and pituitary hormone production remains uninfluenced. These are also called as glucocorticoid directed drugs and example is Mefipristone [29].

Use of osilodrostat for treatment of cushing syndrome:

Osilodrostat is an adrenal blocking agent, and it was initially used for the inhibition of Aldosterone production and to reduce the blood pressure. Basically Osilodrostat is an inhibitor of 11 β -Hydroxylase which contribute to the last step of Cortisol synthesis. Osilodrostat inhibits both CYP11B1 and CYP11B2. A study was carried out to differentiate between the effects of Ketoconazole, Metyrapone and Osilodrostat. It was found that Osilodrostat inhibits cortisol production in HAC15 cells, 18 times more potently than Ketoconazole and 2 times more significantly than Metyrapone [30]. In Phase I and Phase II studies found that the reduction rate of Cortisol levels in the patients by the use of Osilodrostat is very much significant than Ketoconazole and Metyrapone. Also the doses of Osilodrostat are much tolerated by the patients with very little or no side effects as compared to Ketoconazole and Metyrapone.

Conclusion:

On the basis of literature study, it can be predicted that the treatment of Cushing Syndrome requires an immediate, promising and permanent solution. Screening and Diagnostic methods developed for the Cushing syndrome have a high level of accuracy and patient compliance. Despite of having variety of options for treatment like pituitary surgery and adrenal surgery, patients are more comfortable with medication therapy which is very limited in case of Cushing syndrome. The potency of treatment by drugs is very limited and takes very long time to cure causing no surety of successful treatment. Osilodrostat have been shown a great and promising option for treatment in Phase I and Phase II clinical studies. High dose of Osilodrostat is much tolerated in the patients as compared to other drugs like Ketoconazole and Metyrapone. More research is to be done in this direction so as to have a definite and sure treatment option despite of pituitary and adrenal surgery.

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