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KUSHMANDA GRAHONMADA: PARANEOPLASTIC NEUROLOGICAL SYNDROME WITH TESTICULAR CANCER

KUSHMANDA GRAHONMADA: TESTİS KANSERİ İLE PARANEOPLASTİK NÖROLOJİK SENDROMLAR

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Abstract

Unmada (is a broad term which includes various psychiatric conditions) is characterized by deranged mental functions. 'Bhutonmada' (psychiatric conditions of idiopathic nature) is a type of unmada caused by affliction of 'bhuta' / 'graha' (evil spirits or super natural powers). Kushmanda grahonmada (KG) is one among 18 types of bhutonmada. Till date there were no studies have been conducted on KG and the present study aims at better understanding of this condition (KG) along with its clinical utility. KG is characterized by various signs and symptoms like Bahu pralaapam (excessive talking / irrelevant speech / logorrhoea), Ugra vaakyam (verbal abuse / aggression / irritability), Vilambita gatim (slow movements / hypokinesia), Krishna vadanam (hyperpigmentation of face) and Shoona pralamba vrishanam (huge scrotal / testicular swelling). It is very difficult to understand KG based on these few lakshana's (signs & symptoms) described in Ayurvedic texts. KG is a psychiatric condition associated with huge scrotal swelling. Various conditions like 'Paraneoplastic neurological syndromes' (PNS), 'Testicular adrenal rest tumors' (TART), Testicular cancer with brain metastasis', 'Paraneoplastic limbic encephalitis' (PLE), 'Paraneoplastic cerebellar ataxia' (PCA) and other scrotal swellings with psychiatric manifestations resembles with KG.

Keywords: paraneoplastic limbic encephalitis; testicular adrenal rest tumors; paraneoplastic cerebellar ataxia

Özet

Unmada (çeşitli psikiyatrik koşulları içeren geniş bir terimdir), dengesiz zihinsel işlevlerle vasıflandırılmıştır. 'Bhutonmada' (idiyopatik doğanın psikiyatrik koşulları), bhuta' / 'graha' (kötü ruhlar ya da süper doğal güçler) 'in neden olduğu bir unmada türüdür. Kushmanda grahonmada (KG), 18 çeşit bhutonma'nın arasında bulunmaktadır. KG üzerine bugüne kadar herhangi bir çalışma yapılmamıştır ve bu çalışma, klinik durumu ile birlikte bu durumun (KG) daha iyi anlaşılmasını amaçlamaktadır. KG, Bahu pralaapam (aşırı konuşma / ilgisiz konuşma / logorrhoea), Ugra vaakyam (sözlü istismar / saldırganlık / sinirlilik), Vilambita ağ geçidi (yavaş hareketler / hipokinezi), Krishna vadanam (yüzün hiperpigmentasyonu) ve Shoona gibi çeşitli belirtiler ve semptomlarla ilişkilendirilmektedir. Ayurvedik metinlerde anlatılan bu birkaç laksanaya (işaret ve semptom) bakarak KG'yi anlamak çok zordur. KG, büyük skrotal şişlik ile ilişkili bir psikiyatrik durumdur. 'Paraneoplastik nörolojik sendromlar' (PNS), 'Testis adrenal rest tümörleri' (TART), beyin metastazı ile Testis kanseri ',' Paraneoplastik limbik ensefalit '(PLE),' Paraneoplastik serebellar ataksi '(PCA) ve diğer skrotal şişlikler gibi çeşitli durumlar psikiyatrik belirtileri olmaktadır. KG, "PLE"yi özel referans vererek "PNS" ile benzerlik göstermektedir.

Anahtar Kelimeler: *paraneoplastik nörolojik sendromlar; paraneoplastik limbik ensefalit; paraneoplastik serebellar ataksi*

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1. Introduction

Ayurveda possesses eight specialities among them, 'Bhuta vidya' (Ayurvedic psychiatry) deals with diagnosis and management of various psychiatric conditions. The word 'bhuta' has different meanings such as 'super natural power' / 'demon' / 'extra terrestrial force' / 'paranormal force' / 'popular 'mythological personality' etc in different contexts of various classical Ayurvedic texts. 'Bhutonmaada' is a broad term and is characterized by various abnormal behaviours and psychomotor activity seen in a person with insidious onset and idiopathic in nature (Mamidi & Gupta, 2015). Bhutonmada is a type of unmada (psychosis) caused by affliction of 'bhuta' / 'graha'. There are 18 types of bhutonmada's explained in Ayurvedic texts and 'Kushmanda grahonmada' (KG) is one among those (Prasad & Kshama, 2015).

Description of KG is not available in Charaka samhita (Agnivesha, 2008), Sushruta samhita (Sushruta, 2009) and Madhava nidana (Madhavakara, 2012). Only lakshana's (signs and symptoms) of KG are explained in Ashtanga samgraha (Vriddha Vagbhata, 2012) and Ashtanga hridaya (Vagbhata, 2005). The description of KG is similar in both texts (Ashtanga samgraha and Ashtanga hridaya). KG is characterized by the features like Bahu pralaapam (excessive talking / irrelevant speech / logorrhoea), Ugra vaakyam (verbal abuse / aggression / irritability), Vilambita gatim (slow movements / hypokinesia), Krishna vadanam (hyperpigmentation of face) and Shoona pralamba vrishanam (huge scrotal / testicular swelling) (Vriddha Vagbhata, 2012; Vagbhata, 2005). 'Kushmanda' is a Sanskrit word referring to a fruit of the plant 'Benincasa hispida' (ash gourd). KG is named as such due to the huge scrotal swelling which resembles with the size of the ash gourd. Till date no studies have been conducted on KG and it is an unexplored concept of Ayurvedic psychiatry. The present study is focused at better understanding of KG and its clinical utility. KG has shown similarity with various psychiatric / neuropsychiatric conditions like 'Paraneoplastic neurological syndromes' (PNS), 'Testicular adrenal rest tumors' (TART), Testicular cancer with brain metastasis', 'Paraneoplastic limbic encephalitis' (PLE), 'Paraneoplastic cerebellar ataxia' (PCA) and other scrotal swellings with psychiatric manifestations.

2. Paraneoplastic Neurological Syndromes

PNS is a condition which is defined as remote effects of cancer and they should not caused by the tumor itself and its metastasis, or by infection, by ischemia or by metabolic disruptions. Central & peripheral nervous system, neuromuscular junction and muscles can be affected by PNS. PNS can be seen as an isolated condition or it can occur in association also. In most of the patients, the neurological disorder develops before the cancer becomes clinically overt. The most common PNS are Lambert-Eaton myasthenic syndrome (LEMS), limbic encephalitis (LE), retinopathies, sensory neuronopathy (SSN), stiff-person syndrome (SPS), encephalomyelitis (EM), chronic gastrointestinal pseudo-obstruction (CGP), subacute cerebellar ataxia, opsoclonus-myoclonus (OM), and dermatomyositis. PNS are generally caused by various autoimmune processes triggered by the cancer. A subacute progressive clinical course and a severe disability are highly indicative of PNS (Honnorat & Antoine, 2007).

Limbic encephalitis (LE) is one of the PNS and is characterized by confusion, marked reduction of the short term memory, seizures, depression, hallucinations etc which mimics a psychiatric illness. Among LE patients, 20% have a testicular tumor. Ma2-Ab (Ma 2 antibodies) are present in the most of the patients with LE and testicular cancer. LEMS is an autoimmune disorder of the neuromuscular junction which is characterized by muscle weakness and autonomic dysfunction. Opsoclonus is defined by the spontaneous, arrhythmic and large amplitude conjugate saccades occurring in all directions of gaze. It is usually associated with myoclonus of the limbs, trunk, and with encephalopathy. Patients with Ma2-Ab generally develop limbic and brainstem encephalitis with tumors of testes and also with some additional cerebellar symptoms (Honnorat & Antoine, 2007).

3. Testicular Adrenal Rest Tumors

TART's are benign in nature and generally they are bilateral. The location of TART's is within the rete testis. Histologically, TART resembles adreno-cortical tissue. TART's arise from aberrant adrenal cells descended during embryological period along with the testes. TART has the similar histological and functional features of adreno-cortical tissue and growth can be stimulated by increased ACTH (adreno-cortico trophic hormone) (Claahsen-van der Grinten et al., 2009). Bilateral testicular tumors (adrenal rests) may occur in untreated or poorly controlled congenital adrenal hyperplasia (CAH). Psychological abnormalities can be produced by abnormal adrenal or adrenal rest tissue (Keely et al., 1993). CAH is an autosomal recessive disorder occurs due to 21-hydroxylase deficiency. Increased psychiatric morbidity like drug and / or alcohol abuse as well as suicidal tendency was found in CAH patients (Falhammar et al., 2014).

4. Other Scrotal Swellings with Psychiatric Manifestations

Scrotal swellings are common problem among men of all ages. The cause of scrotal swellings may be benign or malignant. Most of the testicular tumors (95%) are germ cell in origin, 4% lymphomas, and 1% other rare histological types (Bromby & Cresswell, 2014).

4.1. Hydrocoele

It is a collection of fluid between the parietal and visceral layers of the tunica vaginalis around the testis. Hydrocoele in adults usually occurs due to the result of imbalance between absorption and secretion of fluid by the tunica. Hydrocoele may be secondary to an underlying testicular tumour. Scrotal swellings can cause considerable anxiety to the patient (Bromby & Cresswell, 2014).

4.2. Scrotal elephantiasis

It is an endemic in tropical regions due to 'filariasis' (Wucheria bancrofti). Scrotal elephantiasis is a condition

characterized by huge scrotal lymphedema with gross deformation of genitals. Even though it is not a life-threatening condition, chronic lymphedema is a disabling with significant physical and psychological morbidity. Scrotal elephentiasis leads to various complications, impaired hygiene, urinary incontinence and also immobility (Brotherhood et al., 2014).

4.3. Giant scrotal lymphedema

It can be caused by obstruction, aplasia / hypoplasia of lymphatic vessels. Most cases of lymphedema are usually caused by an infection. Scrotal lymphedema is due to abnormal accumulation of lymphatic fluid in subcutaneous tissue of the scrotum. Lymphedema is of two types; primary and secondary. Primary lymphedema can be congenital-inherited (Milroy's), praecox / tarda. Secondary lymphedema has three origins, obstructive, phlebitial and angio-neurotic. Peno-scrotal lymphedema generally occurs following an infection or as a reaction to injury. It is a condition leading to progressive enlargement of the scrotum and penis (Rahman et al., 2009).

Inflammatory conditions of the testes like orchitis, epididimitis, epididymo-orchitis; non inflammatory conditions like varicocele, testicular torsion, hydrocele and inguinal hernia are the causative factors of various scrotal swellings (Sehgal et al., 2016). Conditions like hydrocele, scrotal elephantiasis, scrotal lymphedema due to inflammatory origin have not shown any similarity in the signs and symptoms of KG (except scrotal swelling). There is no evidence of presence of psychiatric features in hydrocele, scrotal elephantiasis & scrotal lymphedema etc conditions in literature.

5. Etiology, Pathogenesis, Course and Prognosis of KG & PNS

Bhutonmada is idiopathic in nature and causative factors are untraceable. Pragyaparaadha (intellectual blasphemy) or karma (idiopathic) plays a significant role in the pathogenesis as well as in prognosis of bhutonmada. The onset of bhutonmada is sudden or insidious, without significantly affecting the physiology of the body. The signs and symptoms of bhutonmada is variable and the nature of the condition is multi factorial. The course and prognosis of bhutonmada is unpredictable in nature (Prasad & Kshama, 2015). There is no special description regarding etiology, pathogenesis, course and prognosis of KG described in Ayurvedic texts. The common etiology, course and prognosis mentioned for bhutonmada is applicable for KG also (Agnivesha, 2008; Sushruta, 2009; Madhavakara, 2012; Vriddha Vagbhata, 2012; Vagbhata, 2005).

Para-neoplastic antibodies are the only marker of autoimmunity and they generally do not produce the disease. Cellular immune mechanisms play a crucial role in the pathogenesis of PNS. Till date, no studies have proved that paraneoplastic antibodies are pathogenic. The hypothesis that PNS are immune-mediated remains to be proved yet (Honnorat & Antoine, 2007). PLE is an under diagnosed due to its variability of symptoms and lack of specific diagnostic markers (Voltz et al., 1999). PNS are a heterogeneous group of disorders with huge variability in clinical presentation. The psychiatric characterizations of PNS syndromes remain relatively cursory (Kayser et al., 2010). Thus, variable clinical presentation, uncertain prognosis, idiopathic pathological processes of PNS shows similarity with the etiopathology, course and prognosis explained in the context of grahonmada / bhutonmada.

6. Similarity of Clinical Picture in Between KG and PNS / PLE

Various lakshana's of KG like Bahu pralaapam, Ugra vaakyam, Vilambita gatim, Krishna vadanam and Shoona pralamba vrishanam etc features resembles with PNS and especially with PLE. The similarity in between the signs and symptoms of these two conditions (KG and PNS / PLE) is as follows;

6.1. Bahu pralaapam (excessive speech / irrelevant speech / logorrhoea)

The word 'bahu pralaapam' denotes either excessive speech or irrelevant speech or logorrhoea. There is no evidence of association of scrotal swelling with excessive, irrelevant speech or logorrhoea. Confusion, dementia, psychomotor seizures and hallucinations are the features of PLE (Gultekin et al., 2000) which may cause 'bahu pralaapa'. Autoimmune encephalitis clinically manifests with neurological symptoms such as seizures, psychiatric symptoms, such as anxiety, agitation, hallucinations and psychosis. According to a case report, autoimmune encephalitis clinically manifested with the symptoms of bipolar disorder (Choe et al., 2013). 'Pressure of speech' is one of the characteristic features of 'mania' / 'bipolar disorder' which are similar to 'bahu pralaapa'.

PNS generally involves the central or peripheral nervous systems, resulting in various symptoms ranging from sensory neuropathies to severe and diverse neuropsychiatric disturbances, such as dysfunction in consciousness, cognition, behavior, mood, and perception. Psychiatric changes such as irritability, hallucinations, depression, personality disturbances, and cognitive changes etc are found in PNS. Additionally patients may experience confusion, sleep disturbances, and seizures. Patients with LE have been described various myriad symptoms, ranging from delusional thought content & paranoid ideation to obsessive-compulsive behaviour (Kayser et al., 2010). Mild to moderate dysarthria is found in anti-Ta (Ma 2) syndrome (testicular cancer with PNS) (Somnier, 2017). Even though there is no direct evidence of 'excessive speech' or 'irrelevant speech' in PNS, it seems that the underlying central nervous system pathology and associated psychiatric or neuropsychiatric features of PNS / PLE may cause 'bahu pralaapa' associated with testicular tumors.

6.2. Ugravaakyam (agitation / aggression / verbal abuse)

PNS associated with anti-Ma2 antibodies is characterized

by nervousness and behavioural distrubances (Suero et al., 2017). LE is an autoimmune neuropsychiatric condition, which affects the medial temporal lobe of the brain and is characterized by sub acute cognitive symptoms, seizures, short-term memory loss, and mood disturbances (Neto et al., 2016). According to a case report, a patient of testicular cancer with anti-Ma2 encephalitis and PNS has shown irritability and anxiety (Matsumoto et al., 2007). Mood disturbances such as irritability & depression, panic attacks, hallucinations, unexplained fear, confusion and obsessive-compulsive behaviour etc are seen in anti-Ma2 LE. The association of testicular cancer and anti-Ma2 limbic encephalitis in very strong and due to this strong association orchiectomy or testicular irradiation is suggested even if a tumor cannot be found. LE is characterized by personality changes, cognitive changes, irritability, delusions, hallucinations, paranoid ideations, temporal lobe seizure / psycho-motor seizures and dementia (Kayser et al., 2010). The verbal abuse / irritability / agitation seen in PLE are similar to 'Ugravaakyam' of KG.

6.3. Vilambita gatim (slow movements / hypokinesia)

'Vilambita gati' denotes slowness of movements, which may be due to the huge scrotal swelling or hypokinesia seen in PNS. LEMS is characterized by muscle weakness and autonomous dysfunction (Honnorat & Antoine, 2007). The huge scrotal lymphedema or scrotal elephantiasis causes impairment of free movement due to progressive enlargement of scrotum and penis (Rahman et al., 2009). Gait disturbances and hypokinesis are found in PLE (Kayser, 2010; Gultekin, 2000; Choe, 2013; Somnier, 2017; Suero, 2017). Impaired gait, rigidity of limbs and hypokinesis are found in PNS associated with testicular cancer and anti-Ma2 antibodies. Severe hypokinesis with reduced verbal output has been found in some cases with anti-Ma2 encephalitis. Severe hypokinesis is a very rare phenomenon of para-neoplastic encephalitis. In these patients (with hypokinesis), multifocal abnormalities in substantia nigra or globus pallidus or both has been seen in MRI (Magnetic resonance imaging). Bilateral lesions of globus pallidus can cause Parkinsonism. The hypokinesis and slowness of initiation or completion of movement may be due to the damage of globus pallidus (major output structure of basal ganglia) (Matsumoto et al., 2007).

The clinical clues for Ma2 antinbodies with testicular cancer and PNS are the presence of both hypothalamic (daytime sleepiness, cataplexy, narcolepsy, hormonal deficits and hyperphagia) and brainstem dysfunction (Machado et al., 2012). Atypical Parkinsonism with severe akinesia, facial masking, tremors and rigidity are seen in anti-Ta (Ma 2) syndrome (Somnier, 2017). PCA or subacute cerebellar ataxia is one of the PNS, which may manifests with gait disturbances and hypokinesia (Honnorat & Antoine, 2007). The 'vilambita gati' of KG denotes hypokinesis or atypical Parkinsonism or cerebellar ataxia of PNS or impaired movement due to huge scrotal swelling.

6.4. Krishna vadanam (hyper pigmentation of face)

The word 'Krishna vadanam' denotes either hyper pigmentation of face or dark complexion of face due to underlying disease. In 1% of internal malignancies, skin provides the first clue for diagnosis. Skin manifestations of internal malignancies may be due to direct effects (due to the invasion of the skin by a tumor or its metastases) or to indirect effects (which triggers the cutaneous signs or symptoms). Some of the skin manifestations occur as a part of complex PNS. PNS affecting the skin may precede the manifestation of the tumor, but sometimes they may also manifest at much later time. Malignancy is one of the multiple causes which cause diffuse or focal darkening (which is a distinctive skin sign) of the skin. The hyper pigmentation in such cases is diffuse and profound in exposed areas such as face, neck, back of hands, areas affected by trauma, areas subjected to slight pressure, and mucous membranes. Pigmentary changes have been linked to the production of the polypeptide lipotropin, which can induce the production of MSHs (melanocyte stimulating hormone), which in turn, stimulates the production of melanocytes in the skin. Association of ACTH syndrome and reproductive organ tumors is well known. Elevated plasma cortisol and corticotropin levels indicates ACTH syndrome. Hyperpigmentation is a nonspecific cutaneous manifestation of leukemia, Hodgkin and non-Hodgkin lymphomas (Yuste-Chaves & Unamuno-Pérez, 2013). Based on these findings it seems that 'krishna vadana' mentioned in KG can be seen in a case of testicular cancer with PNS.

6.5. Shoona pralamba vrishanam (scrotal swelling)

As discussed in the previous sections, the scrotal swelling may be due to various inflammatory and non-inflammatory causes. Scrotal lymphedema or scrotal elephantiasis, hydrocele, inguinal hernia, testicular tumors (malignant or benign) and TART etc are the causes for scrotal swellings. 'Shoona pralamba vrishana' denotes painless scrotal swelling which indicates towards a non-inflammatory (tumor or lymphedema) pathology. By considering all the above facts it seems that the lakshana's explained in KG denotes a scrotal swelling (mostly tumors) with associated psychiatric features (PNS or PLE or PCA). No other bhutonmada (except KG) is associated with scrotal swelling.

7. Conclusion

'Kushmanda grahonmada' is one among 18 types of bhutonmada. KG is a psychiatric condition associated with huge scrotal swelling. The signs and symptoms of KG have shown similarity with various conditions like 'Paraneoplastic neurological syndromes' (PNS), 'Testicular adrenal rest tumors' (TART), Testicular cancer with brain metastasis', 'Paraneoplastic limbic encephalitis' (PLE), 'Paraneoplastic cerebellar ataxia' (PCA) and other scrotal swellings with psychiatric manifestations. Among these conditions, KG has shown striking similarity with 'PNS' with special reference to 'PLE'.

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