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Review Article

BIOLOGY OF HEAD AND NECK CANCER PAIN

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ABSTRACT

Pain is one of the most common presenting complaints in patients with advanced cancers occurring in about thirds of the patients at the time when they are first diagnosed to an average of 60-100% of the patients in the terminal stages of the disease process. Oral cancer is the sixth most common malignancy in both sexes in the world and the third most common malignancy in the developing nations. Among these, about half of the patients die within five years from the day of diagnosis while the ones who survive are left with severe functional and aesthetic compromises. Despite all these complications and the significant morbidity and mortality associated with this deadly and to-happen consequences, cancer-associated pain is one of the most common situations difficult to manage in a significant number of cancer affected patients. Despite all the advances in the understanding, diagnosis as well as treatment modalities available for the treatment of cancer associated pain, a significant fraction of patients are left to bear considerable pain owing to the lack of an exact criteria for the evaluation of pain, reluctance of the health care providers regarding the use of opioids and the reservation of advanced treatment modalities for the management of pain only in its advanced or terminal stages.

Key Words - Head and neck cancer pain, nociceptive / neuropathic pain,algesia / hyperalgesia.

INTRODUCTION

The International association for the study of pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

Pain, infact, is described to be a protective sensation and/or reflex of the body as it alerts an individual towards a physical injury and/or some disease process going on in the body as described by Sherrington as the physical adjunct of an imperative protective reflex.[1, 2]

DIAGNOSING HEAD AND NECK CANCER ASSOCIATED PAIN – A DIAGNOSTIC DILLEMA

Assessment of the head and neck cancer associated pain is often considered as a challenging task for the health-care providers owing to its multi-factorial etiology as well as the modification of the essential pain components, objective as well as subjective, depending on the actual sensation of the pain as well as the reaction of the patient due to a variable perceptive component secondary to a number of defined and can't be defined criteria.[1,2] The majority of the head and neck cancer associated pain is because of the direct impact of the growing neoplasm accounting roughly around 83% while the rest of the 17% of the cases reporting with pain due to the secondary effects of the anti-cancer therapeutic regimens.[3]

PAIN PERCEPTION VERSUS PAIN REACTION

Pain basically is composed of two essential components-the first component being the actual sensation as perceived by the central nervous system and the second component, being the reactionary, subjective component that actually influences the patient's perception of pain.The psycho-social aspects, depression, anxiety and fear, mental isolation, other unrelieved symptoms and the actual sensation of pain itself in this particular group of patients, all lead to the exacerbation of the total experience of pain.[1, 2]

WHY TO KNOW THE BIOLOGY OF CANCER PAIN?

The exact assessment of the type and cause of the pain becomes important since the former helps in providing the appropriate symptomatic therapy for the pain while the latter helps in the appropriate treatment required controlling the underlying causative disease process.Understanding the complex pain pathways is, infact, a cumbersome task involving multiple neurotransmitters and interlacing pain pathways with bare nerve endings acting as the peripheral pain receptors. These free nerve endings are further of two types that are described to conduct pain sensation via two pathways. Among them, comes first, the primitive of the two, the so-referred paleo-spinothalamic pathway that carries afferents for painsensation via the slow-conducting C-fibers with conduction velocity of about 1m/second and substance P as the primary neurotransmitter while evolutionary the more recent one, the neo-spinothalamic pathway carrying the afferents for pain via the fast-conducting A-delta fibers with a conduction velocity of around 15m/second and glutamate as the primary neurotransmitter.[1, 2]

EMOTIONAL COMPONENT OF PAIN

The emotional component of the pain, an essential component of head and neck cancer associated pain is explained on the basis of the fact that on their way to the central nervous system, important collaterals from the pain pathway are given to the components of the limbic system, the so-named amygdala complex.[1, 2]

ALGESIA AND HYPERALGESIA

Also, the perception of the pain is at two distinct levels. The first perception of the pain sensation is at the sub-cortical level at the level of the thalamus and this perception of the pain is responsible for the sensation of crude pain. The higher level of pain perception is at the cortical level which gives the final perception of the actual sensation of pain with all its distinctive characteristics. Sometimes, the pain threshold gets lowered, the exaggerated sensation and/or perception of pain being referred to as hyperalgesia.

Further, the different types of pain include the fast and slow pain carried by the A-delta and C fibers respectively. The fast pain is perceived immediately after a trauma or injury in a well-defined anatomic region either due to the noxious stimulation of the peripherally located bare nerve endings or due to neural compression secondary to pressure effects owing to cancer associated growths or edema due to secondary infections around a nerve trunk, being carried by the A-delta fibers, taken over by a more diffuse, dull and intense pain sensation, carried by the C fibers.

Also, the pain sensation can, further, be of epicritic or protopathic nature with the former type of pain showing low threshold but accurate localization while the latter type exhibiting a high threshold but with poor localization, the one more commonly seen in association with head and neck cancer associated pains.

Further, the pain sensation perceived can be superficial or deep, based on the structures from where the pain sensation arises with the pain sensation arising from the deeper structures like muscle, bone or periosteum and tendons being called deep pain, poorly

localized and the one arising from the superficial structures as skin being referred to as superficial pain and usually well-localized, based on the anatomic level of invasion of the cancer associated growths.[1, 2]

WHAT THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN SAYS?

The scheme proposed by the International Association for the Study of Pain categorizes pain according to five different axes-the location of pain, involved organ or tissue, the temporal pattern of pain, pain intensity and the time since the onset of pain and the prime factor-the etiological factor/factors behind the origin of pain.The IASP scheme, however, does not distinguish formally cancer pain from the non-malignant causes of chronic pain or do other diagnostic schema advanced by the US Department of Health and Human Services and/or the World Health Organization.[1]

The classification of cancer pain may and does have important diagnostic and therapeutic implications; hence, a distinct taxonomy of cancer pain is highly warranted for the effective assessment, gradation and management of this unique group of multi-etiological pain in the advanced stages of cancer management.[2, 4]

VARIOUS SCHEMES FOR CLASSIFYING HEAD AND NECK CANCER PAIN

Etiologic classification

Based on the proposed etiology of the causation of head and neck cancer associated pain, it can be classed as the one which is primarily caused by cancer, either because of compression or infiltration of pain sensitive structures, invasion of bone, nerve and/or muscle; or the pain that is caused as a consequence of the various treatment modalities used for treating cancer; pain caused due to disabilities in the form of post-herpetic neuralgia; and pain that is un-related to cancer or the one arising as an after-math of the therapeutic approaches used for treating cancer or the pain that is perceived as a result of some other concurrent pathology in the form of arthritis, migraine or neuropathy etc.

Patho-physiologic classification

Based on the patho-physiology of the pain sensation, it can, further, be classed as nociceptive and / or neuropathic or the one that is of confounding or mixed pathology along with the one that is purely psychogenic in origin.

Temporal classification

Based on the temporal basis of pain, it can be classed as acute, breakthrough or chronic pain.[5]

Classification based on the severity of pain

Last but not the least, pain sensation perceived is graded and based on the severity of pain as mild, moderate or severe.[4-6]

Most of the head and neck cancer related pain is caused due to the effects of cancer itself. The uncoordinated growth pattern revealed by the growing neoplasm often leads to pressure effects on the subjacent structures and/or infiltrate the pain sensitive structures or invade the bone, nerve and/or muscle leading to the onset of pain sensation.

Locally invasive and erosive cancers directly produce tissue destruction and/or nerve compression evoking the pain sensation.[7, 8]

Recent studies have indicated pain mediating inflammatory cytokines to be either released from the growing tumor or from the surrounding tissues in response to tumor invasion and/or metastasis as in cases of secondaries in jaw bones from the metastatic spread of cancers of the breast and/or prostate.[9, 10]

Again, injury to the nerves, central or peripheral, results in multiple alterations in the pain mediating pathways in addition to the direct irritation of the bare nerve endings coming in contact with the pain mediating cytokines.[11,12]Also, sometimes, the depolarization threshold gets lowered and nerve impulses start generating spontaneously, so-called hyperalgesia as already described. An ongoing cause of pain in the periphery, then, results in multiple changes at the spinal cord level magnifying the perception of the actual pain with the expansion of the receptor field due to facilitation and/or sub-liminal fringe effect on the cells of SubstantiaGelatinosa of Rolando lying in the dorsal root ganglion. This occurs partially via calcium influx into the cells, a factor considered significant since many analgesic medications act by blocking these calcium channels at the level of the spinal cord. Activation of the normally inactive NMDA-N-methyl D-aspartate receptors is another crucial step that amplifies the pain response-the NMDA receptors being other important targets for the cancer pain relieving analgesic medications.[13]

IATROGENIC CANCER PAIN

Another important cause of head and neck cancer associated pain is the pain that is produced as a consequence of the various treatment modalities being used in the treatment of the primary pathologic process.[14] These types of iatrogenic pain sensations can be perceived either in the form of acute pain or the discomfort following surgery or other invasive procedures or in the form of various post-surgical chronic pain syndromes and/or pain due to unintentional severing of peripheral nerves.[7, 14]

The use of radio-chemo-therapies can, also, lead to severe type of pain perceived as a result of radio-chemo-therapy induced mucositis, secondary opportunistic infections in the form of candida and herpes simplex viral infections and /or peripheral neuropathy.[15-17]Oral mucositis is a therapy and rate-limiting complication of cancer chemotherapy as well as head and neck radiation therapy.

Moreover, many chemotherapeutic agents are well known for their adverse drug effects in the form of peripheral neuropathy.[18] Radiation therapy may, also, compromise blood supply to vital tissue structures, decrease healing capacity, injure soft tissues and/or neuronal structures resulting in mucositis , osteoradionecrosis and peripheral neuropathies.[15, 16, 19]

To make conditions even worse, musculoskeletal pain is rather a common complication seen in patients following treatment for head and neck cancers.[9, 10, 20, 21] The common etiologies for pain perceived in such patients include the effect of the tumor on the underlying and subjacent structures, pressure effects, post-surgical and/or post-radiotherapeutic complications including various grades of jaw resections, secondary scarring and/or fibrosis and contractures along with secondary temporo-mandibular joint changes.[15, 16]

In the end to summarize, it can be said that a significant number of cancer patients often have more than one identifiable patho-physiologic type of cancer associated pain. One study highlighted that a group of 31% of cancer affected patients suffered from mixed nociceptive and neuropathic types of pain.[12] In another similar study conducted by Ashby and colleagues, 79% of the patients suffered from two or more patho-physiologic types of pain.[1, 2, 6, 7]

PSYCHOGENIC PAIN

A Grave confounder- Psychogenic pain is another important cause of pain often making the life of cancer patients even more miserable and arrived at; largely by the diagnosis of exclusion.[22] Although a crude task, psychological basis of pain alone can hardly be associated with most of the cancer associated pains. Conversely, however, the role of psychogenic pain as a compounding and/or aggravating component affecting the patient's actual perception of pain can again hardly be ruled-out.

BREAKTHROUGH PAIN

A therapy-associated concept of pain- Another significant term used in descriptions of cancer associated pains is the breakthrough pain that is the pain that indicates the flare-up of discomfort in patients in whom the base-line level of pain is well-controlled by the round-the-clock analgesic regimen.[23-25]

The severity of cancer pain is of help in reflecting the size of tumor, its localization and the extent of tissue destruction. The mechanism of pain is also an important determinant in the characterization of pain as metastatic bone lesions and neural injuries are notoriously

more severe than the pain arising as a consequence of a slow growth of a neoplasm.[9, 10, 21]

PAIN GRADING SYSTEMS

The intensity of pain felt is often used as a guide for the appropriate therapeutic strategy to be followed. Valid tests to quantify the intensity of pain include the so-called VAS or visual analogue scale with word descriptors from no (0) to excruciating (10) pain, numerical rating scale, verbal descriptors of pain severity or Verbal Likert Scale using terms like none, mild, moderate or severe for the description of pain.A similar scale is used for the quantification of pain in children and patients unable to express the intensity of their pain with five grades or facial expressions with smiling (0) to eliciting a cry (5) intensity of pain.[1, 2]

HEAD AND NECK CANCER PAIN

A Dynamic Clinical Experience

Another significant factor affecting the management of head and neck cancer associated pain is its dynamic nature with the intensity of pain fluctuating during the course of the disease as well as the institution of treatment, thereby, making it mandatory to re-evaluate periodically and determine the severity of pain.

Information regarding the pain including its localization, character, severity, onset, and duration, temporal pattern, relieving and aggravating factors, associated symptoms and previous analgesic therapy and any history of prior anti-cancer treatment should well be obtained.[2]The patient's psychological state including the presence of anxiety, fear or depression should also be assessed.[22] The most important parts of the physical systems include the evaluation of neurological and musculoskeletal systems.

Serum tumor markers may be of significance in the assessment of the exact extent of the tumor along with a high prognostic significance and the detection of any secondary or metastasis in association with the primary tumor or any recurrence of the tumor. Various imaging modalities can also be used to arrive at a particular cause of cancer associated pain depending on the situation.[26]

CONCLUSION

The aim of this paper is to highlight the varying etiologies and patho-physiologies of the head and neck cancer associated pain and more than that the need for an effective pain management protocol to be followed in the management of the variable expressions of this type of pain in patients who are made and/or left to suffer and live a life full of agony of pain despite the availability of voluminous literature regarding the understanding of cancer associated pain.

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