Insensitivity to pain due to Genetic Mutation

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ReviewArticle

Abstract

Pain is neuroanatomically, psychologically and neurophysiologically complicated and its first function is protecting all alive creature body. This issue is so questionable and interesting that people who don't feel pain how face this sensation and what problems threaten them. So many researchers by using 73 references, articles from electronical and library references have done a clinical study about CIPA which is a rare disorder of neuropathic disorders. These patients have no sensation toward pain and paiful stimulations and no sweating. This disorder has been occurred by genetic mutation and has been under study from 1996 to 2012. Which un health – care tream can reduce their complications by early diagnosis and thereaputic and preventive interventions.

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Introduction:

Pain is a conscious feeling and emotional unpleasant experience followed by potential and real tissue injuries or any hurt (1-5). Feeling pain is very complicated from the Stan point of neuroanatomy, neurophysiology and psychology (4-10).

The first function is to maintain the factors threatening the entirely of living creatures. Despite pain is unpleasant, it is a warner, because by sending the massage, it informs that the hurt is approaching (11). Some people believe that this warning is ineffective, insufficient and sometime incorrect in some cases, because since it appears that the disease such as cancer has developed. Moreover, many humans are afflicted with chronic pains haunting them for years (12).

According to scientists study, the various influential parts on feeling pain function in three Levels include: 1. Sensory-discriminative, 2. Affective-motivational and 3. Cognitive-evaluation (13,14). In cognitive level, the individual suffers from depression, this stimulation conducts him/her to take next steps to avoid the hurting factors. In biological level, pain function is in a way that the person moves automatically and maintains him/her self against the hurting factor by cognitive activity (12).

Feeling pain sending system begins from the pain physiologic-sensory receptors which is located at the end of peripheral nerves. The feeling pain receptors are located in skin, joints, Muscles attached to bones, tendons, Cornea, viscera and other more susceptible organs to injury (12-23).

After damage, prostaglandin and similar materials are released from the tissue which reinforce the sending process (4).

Transferring the pain massages is done from two main ascending ways in spinal Cord: 1. External pain system related to discriminative sense of pain ended in outer cores of thalamus and cortex 2. Internal pain system related two affective-motivational responses ends up in inner core of thalamus and anterior cingulated gyras (Cingulate gyros cortex 10) and insulan 11 (23-27). Disorder in each of routes leads to defect in apart of feeling pain system (26). The massages in posterior horn of the spinal cord are adjusted and balanced carefully. Feeling pain is intensified and stopped (28). The interneurons 12, neurotransmitters 13 and chemical material like opioid endogenous (endogenous opiates) 14 cause the massage sending signals to reinforce or to decline (4). By activation of connected networks, the massages are sent to upper regions. The place of these regions is between amegadla 15, hypothalamus and the brain layer. Then the massages are interrupted by the network in the brain layer including insulin anterior cingulated gyras and some other regions (3,6,28-31). These regions connect to pain experience by increasing their activity (26).

Sensitivity to pain is human characteristics and is presented as haplotyp in 96% of them. It means that the individuals in sensitivity to pain are divided into 3 categories: Low, medium and high sensitivity. This sensitivity is based on the activating enzyme gene, catecholamine –o–methyltransferase.

(COMT) whose rate is higher in people with low sensitivity (6).

Scientist have discovered 70 – 150 thousands of genes effective on creating and perceiving pain.

(23) these genes data are concerned with nociceptive system including to create, transmit and react to painful stimulations (27,30,31). These stimulations can be mechanical, thermal or chemical which include mechanical pressures, high temperature, cellular injuries and inflation (31-33).

The genetic mutations can cause disease-like changes in feeling and sensitivity to pain. A limited number of genes can prevent pain (27).

Insensitivity to congenital feeling pain are generally two forms:

1. in sensitivity to pain in which the person can not describe the pain intensity and type.

2. Indifference to pain in which the person perceives the pain but can not get rid of the painful factor (9,10,31). One of the diseases type 1 is congenital insensitivity to pain with anhidrosis (CIPA) which is randomly diagnosed as a case report in a few people. This is why the genetic screening in the patient and his/her family is done after diagnosis.

This disease is unknown for the patients, their parents and medical employees due to scarcity (34). This issue is very interesting and questionable for individuals who know these patients, and like to know how they face insensitivity to pain and what problems they have? (27)

In some reference books about children, a summary of materials are rarely written about the disease, moreover, in Iran a few number of researches and as case report have analyzed the disease state and epidemiology (23). While in recent years due to being interesting and the studies based on it, the different countries are surveying and recognizing it rapidly. Therefore, the researchers. By entirely review and comprehensive study and emphasis on its genetic mutations, intend to take action to more recognition of this disease for medical profficianal personnels.

Intruducing the Disease:

Congenital insensitivity to pain with anhidrosis (CIPA) is hereditary sensory-autonomic neuropathy type V (HASAN) (36-38). Which its cases are reported from all over the world (11,34,35,36,39), the neurologists consider it as a rare disease, and the occurrence probability was estimated 1 from 125 million people (39) Most patient were male (36,37).

The first time, Steinbach diagnosed this disease in a mother with her 7 children and her aunt and stated the disease criteria including existence of disease from birth, not being acquired insensitivity to pain (in other words it not be secondary to disease or damage) and lack of retardation of the patient (31).

No exact information about its prevalence and presentation rate not been reported until today (30,32).

In medical articles, 60 cases until 2006 (40) and 100 cases until 2009 afflicted with this disease have been reported as a case report world wide. Which all are in pediatric age (35) and it has a high outbreak in japan and Israeli Bedouin abnormally (5,31,36,37).

The highly reported cases for this disease in Israeli Bedouin is due to the propinquity marriages and it is posed that these individuals are the carriers of the disease gene formed as homozygote (35,41).

But, by reviewing the articles, it is found that the statistics are different so that more than 300 cases in Japan, 84 cases in USA. (11), 28 cases in Israeli Bedouin (9,33), 5 families in Finland and 30 cases Quebec province in eastern Canada and a case in Newzland (30,41-43), 6 patients of a family in Sweden, 40 cases in a village in southern Sweden (44), 2 cases in morocco, a case in China (45), a case in turkey (45), a case in Saudi Arabia (47), 2 cases in Nigeria (46), 5 cases in Iran including a case from Aryan – Indian (34), 2 cases by Iran surgeons association, a case in Mazanderan and a case in shiraz have been reported.

Physicians and investigators reported that these patients expressed the disease presentation by full insensitivity to pain in the whole body without reaction to painful stimulations (11,29). And expressed that in this disease, high secretion of endorphin in brain cause the response of the receptor sensitive to pain to decreases (27).

These presentation are diagnosed firstly in infancy (31,48,49). These patients endure the injury in soft and tough tissues well (33), and perform the occurrences which are painful for others, with no reaction. Sometimes these damages are created by child and he takes pleasure. For example, he/she bites his/her tongue or injures him/her self in a public place with a knife (27) and causes self – mutilation or auto amputation (31).

One of the current clinical symptoms in the patients sections of tongue and lips (30), this action begins immediately after teething and it is a good symbol to diagnose rapidly. Teeth decay is without pain and he patient loses his/her teeth very soon before learning how to chew (11,29,31,35). Other observable symptoms include, burning growth disturbance (32), vascular necrosis (32), orthopaedic problems and symptoms.

Guider et al (34), (1998) expressed that sprain, fracture, joint symptoms and ends necrosis with spontaneous loss of fingers and toes, chronic infections in bones and joints, multiple scares (35), osteomyelitis (36), Charcot's joint (37), scoliosis (39) and joint deformation are the most major orthopedic complications of the patients (48).

Also, the surgeons facing these patients have expressed that the orthopedic problems become the auto amputation factor with surgery (11,30,48-52).

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Also, eye specialists in a study about mentioned patients have found that optic damages and cornea infections was seen due to external solids entrance to eye balls. The cornea reflex decreases or completely destroy.

In these children, there was no symptom of infection the lack of affliction infection presentation is of surprising symptoms in these patients. For example appendicitis inflation (40) is diagnosed leading to peritonitis inflation (11,41).

An other characteristic of this disorder except inability in pain sensitivity is inability in sweating to cool the body, when they are in hot environments, their body temperature increases which is recognized to be due to disorder in Akron glands (53). Not sweating in body and upper organs is seen in 100% of the patients but it is different in other sections (36,54,55).

According to recent studies on these patients, it is seen that there is no olfactory and gustatory sense, temperature and vibration which are usually normal (56).

It is worth mentioning that, although most researchers believed that these patients were healthy evolutionarily and intelligently (5,7,9,10,29,32,57,58) and they had normal speaking (60), Big man (2009) expressed that these children suffered from severe or medium mental retardation that this issue along with insensitivity to pain causes auto amputation (2,35).

Hypotonia 40 is seen in the first years of life, but muscle strength will improve in next years (54,55).

Other patient problems in childhood have been reported behavioral problems, irritability, hyperactivity, impulsivity, and acting–out behavior.

Pathophysiology:

From studies on these patients, it is determined that this disease gets central and peripheral nervous system involved (53).

Although the exact pathophysiology of the disease is uncertain until now (59), but some scientists consider it as familiar (affliction of several children from a family) b (11,29,44,45) and others consider it as genetic (family propinquity between the parent) (2,5,7,32). But most reports state evidently that this disease is transmitted as autosomal recessive (2,5,7,32,59-60).

Also a combination of biocimical and biological assay has shown that polymorphisms (25,29) and pathologic genetic mutations lead to the disease (29). This mutation is related to gene T-ins -1926, receptor tyrosine kinases (RTks) for nervous growth factor (NGF) (26,33,35,39,50,51). Two genetic mutation G571R and R774P lead to inactivate the receptor NTRK1 in auto phosphorylation process.

These mutations lead to: 1. Inactivation of the receptor gene NTRK1 along with prevention of auto phosphorylation process. 2. Effect on gene of the receptors of nervous growth factor. These genes influence the voltage of sodium canals (29). The sodium canals in nervous system send nervous massages arising from physical damages to brain (4). In recent study in japan on 31 patients from different groups, five more genetic mutations are discovered which prevent autophosphorylation in nervous and non-neuronal cells including: G516RT, R643W, R648C, G708S, G571R (31).

The studies by Miranda et al. (2002) have shown that the genetic mutations through two mechanisms cause the disease: 1.created mutation in receptor neurotraphic tyrosine kinas type 1.

2. Decreasing the activity of these receptors (29).

Bigelman (2009) has obtained new findings concerned with the genetic mutation and state that molecular defect in the receptor TRkA/NGF can considerably prevent activity of chemotaxis neotrophils and cause high susceptibility to infections (31).

Although phenotype of the patients has been known well (33), Providing the map of their genotype has shown that disorder in position 13.7Mb on chromosome 2q.Genes screening in this region is the indicator of protein mutation on SCN9A (23,30,43) which Leads to decrease the receptor function (29,61). Nervous fibers conducting heat and cold are not evolutionary (11). The number of small myelinated nervous fiber and natural unmyelinated ones has declined. (27,53,58-60).

Bigelman (2009) has discovered the place of defect on chromosome 1 (1q21-q22).

In analyzing two CIPA patients, the researchers found randomly a hidden nervous system separated from sense and touch nerves. This sensory system is located along vein wall and sweat glands. Although it was expected that it had a role in unconscious sense, surprisingly it was determined that when the focus is removed from sense nervous ends of natural skin, this system functions consciously.

It means that tactile sense is disrupted severely and the individual can react to different temperatures and physical contact. However, these patients can fell cold or hot, harsh or soft objects through remained nervous ends. Therefore, they will have enough sense to spend their daily lives (33).

Diagnosis:

To diagnose this disease, Scientists confront a lot of pitfalls due to its much various presentations and lack of diagnosis by simple tests (2). They consider clinical symptoms as the most important diagnosis method, the other suggested diagnosis approaches based on different surveys include:

1. Neurological examination including threshold of sensitivity to pain in somatosensory using pain full stimulations, hot or cold objects.

2. The analysis of autonomic function (6,39,52).

3. Sweat test.

4. Intradermal histamine test (39,62).

5. Cerebrospinal fluid analysis (to measure endorphin and encephalin), electrophysiological test (to determine the rate of consuming naloxone to

ascertain the rate of insensitivity to pain) (31,39,53),

6. Histological analysis with the study of skin (57).

7. Skin biopsy and Leight microscopic sural nerve biopsy (full destruction of myelin in nerve fibers transmitting pain, heat and autonomic function are seen) (31,32,39,53).

8. Neuropathology and neurophysiology (39).

9. Analyzing urine from ejaculating un known combinations (29).

10. Genetic molecular analysis test.

11. Genetic map (31,32,39,43), 13-Ultrasonography, 14.Magnetic resonance image (M.R.I) and finally.

12. Autopsy

Also, the diagnosis in families with genetic mutation before birth and in pregnancy, DNA test from amniocentesis in 15-18 weeks of pregnancy and chorionic villus sampling in 12th week of the pregnancy (39,41) are used.

Treatment:

This rare disease has been untreatable until today and there is been no effort to treat, and only its various consequences and problems have been subjected to treatment which is hardly feasible (49,50,58). In order to support treatment, it is suggested that the treatment team in cluding eye specialist, dentists and orthopedists cooperate together.

From the done study in treatment, consuming naloxone to improve transmitting the massage in nerve cells and morphine –like –pain- inhibitory done by Axelrod (2007) and Bar (2009) are taken into account (39).

In study by Big man (2009) and Bar et al, using antibiotic immediately and removing and disinfecting infected tissues by surgical debridement is suggested to prevent from developing infections to deep tissues are considered (35,56).

Killic et al. (2009) examined consuming intravenous immunoglobin to treat hypogammagloblinemia and faced positive results (46).

Albus (2005) indicated that effective management of treatment is increasing public information to rapid diagnosis, establishing a committe to support patients, genetic consulting and screening, preventing probable symptoms, support treatment of fractures, surgical interventions for deformations (2) including corrective osteotomics, shortening by epiphysiodasis or shoe Raises and Braces. In optical disorders, keratoplasty, corneal patch graft, tarsorrhaphy, optical bandage have been suggested (56).

Egzel roud (2009) suggests that the behavioral disorders of children is controlled using antipsychotic and/or attention–deficit/hyper activity disorder (ADHD) medication.

Egzel roud (2007) suggests that children's milk-teeth be pulled out after sprouting so that the child cannot bite his/her tongue, lip and fingers until she/he grows up and learns not to chew these parts. The permanent teeth should be ejected as well.

Prognosis:

Regarding occurrences arising from important health problems in children and followed by mortality and disability, these children may die due to trauma and numerous damages in the first years of their lives. Hyperthermia is the most important infancy problem. So, 50% of the patients will die before the age of 3 due to high temperature of the environment and most patients barely survive up to 25 (35).

Rozentsveig et al. (2004) in I srael and Weingarten et al. (2006) in USA, by researches on patients respecting anesthesia techniques and symptoms prevalence after operation determined that the most operations on them were orthopedic, nerve biopsy and optical operation.

They stated that these patients were able to endure or thopedic large operations without receiving an aesthetic and sedative after the operation. Nausea after the operation and hyperthermia didn't present in any cases, but there were symptoms such as hemodynamic, hypothermia and cardinal problems and cardiac arrest after the operation (31,53,62).

The Intensitive Cares:

The care of these children includes: adapting the child and family to the disease, preventing from presentation of next di orders, knowing them at birth ,training the preventive ways from

injuries, daily examination by family and school nurse (9,10,49) that the primary symptoms including infections are diagnosed soon, and treated punctually and sufficiently (31).

The steps to solve these problem consist of: providing feasilities for welfare, comfort and easement of the child and their family (49), avoiding dry hot climate and sport and severe activities, exact control of the body temperature , cooling the body by water acetaminophen or ibuprofen if fever presents, protecting the child from damaged using helmet, attention to teeth decay and tongue, fingers and toes injuries by protective tools (24,25), awareness of homodynamic and hypothermia after operation by heating. These symptoms are controlled by doing rapid steps (26,52,62,63).

Conclusion:

Infant birth with congenital insensitivity to pain and sweating are along with various problems. So, prevention, diagnosis, symptoms, treatment and parents, child and careers training, free and permanent relationship with them, taking care of the child and family states by nurses and practitioners will play an important role in declining the disease symptoms. These children can have a natural life by respecting limitations.

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