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Presence of neuropathic pain as an underlying mechanism for pain associated with cold weather in patients with sickle cell disease

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Introduction/Background

There are several conditions in sickle cell disease that are associated with pain, [2][3][4] [5] [6] however, the association between weather changes, more specifically and consistently exposure to cold, and pain has alluded a clear explanation. The association of cold and pain in SCD was first suggested by Graham in 1924.[7] The phenomenon of weather changes and worsening pain in SCD is worldwide in scope suggesting a common underlying physiology. It has been reported in the US,[8][9] Africa,[10][11] Jamaica,[12] and the UK.[13] Not all of the investigators found an association between painful episodes and weather changes,[14] whereas others have found an association between worsening pain with some factors but not others.[8][9] However, patients, and their family members are well aware of these associations.[6][10][15][16]

Various hypotheses have been presented to explain how changes in temperature, exposure to the wind, or climatic changes precipitate pain. In 1971, Addae suggested that a redistribution of the circulation during exposure to a cool environment reduced blood flow to areas, including bones, leading to sickling and local ischemic changes in the area effected.[17] Serjeant too suggested that this painful response to cold is a form of a “steal” syndrome,[18] and that blood is diverted from the bone marrow when skin is cooled, and this results in a painful episode. An explanation offered for higher wind speed being associated with an increase in hospital admissions for painful episodes was due to skin cooling secondary to evaporation of sweat, though an explanation of why skin cooling would cause pain was not offered.[13][9] None of these hypotheses have been adequately confirmed. Is there a plausible physiologic explanation that would account for this observation, and perhaps allow

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us to improve our patients' lives by providing better suggestions than to avoid exposing too much skin to windy or cold weather?[13][9][19]

Hypothesis

We suggest that there is a physiologic explanation for sickle cell pain that is associated with cold weather. As a result of persistent or frequent recurrent nervous stimulation and/or damage, possibly due to repeated vascular tissue damage, those who have these symptoms, have developed a dysfunctional nervous system, resulting in neuropathic pain, and that these hitherto unexplainable pain symptoms are in fact allodynic and hyperalgesic responses.

Evaluation of the hypothesis/idea

In order to support our hypothesis, it is necessary to reexamine the pain experience for those with SCD. Pain in sickle cell disease starts after the first few months of life, when the switch from fetal to adult hemoglobin occurs.[20] The first painful event is frequently due to dactylitis, and as children get older, they have more frequent episodes of pain. The largest study to report the clinical events of infants and children with sickle cell disease is the Cooperative Study of Sickle Cell Disease, in which investigators followed almost 700 infants and children by monitoring clinical events during their first decade of life. For those with hemoglobin SS disease, investigators found that the incidence of a painful event (defined as one that required the subject to be brought to the medical center for care, thereby likely underestimating the true incidence of the pain events) went from 2.9 events/100 persons for those less than 6 months of age to 9.5 events/100 persons for those between 6-12 months, to a high of almost 41/100 persons for 5-year olds, with the rate close to 40 events/100 persons for those 6-10 years of age.[21] The rate for those with hemoglobin SC disease was lower, but ranged from 15 to a high of 40 events/100 persons between the ages of 3-10 years. Importantly, these rates do not include the incidence of episodes of hand foot syndrome, another painful syndrome, which is pain and tenderness, with or without swelling, in the hands and/or feet of a child less than 10 years old. For children with hemoglobin SS disease, hand foot syndrome was 14.6 events/100 persons for those younger than six months, peaking at 31.3 events/100 persons for those aged 6 months to 1 year.[21] The number of hours or days that the pain lasted for these events is not reported, but it should be remembered, that throughout this entire time, pain pathways are active.

Others studying pain in children and adolescents with sickle cell disease have found that patients experience pain on 30% of days, and the pain was managed at home 90% of the time.[22] They also found that older patients had longer painful episodes.[22] Dampier found in a diary study of children and adolescents with sickle cell disease who managed their pain at home, that they were experiencing some type of pain on almost 17% of the study days.[23] Maikler, et al. also found that children reported pain on approximately 17% of the days, and adolescents experienced pain on 20% of the days.[24]

The pain experience in adults is at least as severe, if not more so, than in children and adolescents. In 2008, Smith et al, reported on their prospective study of 232 adults with sickle cell disease whom they followed for up to six months, using a daily self-reported pain diary. They found that subjects reported pain on more than 50% of the days, and almost 30% experienced pain on more than 95% of the study days.[25] A clear picture emerges that for substantial periods of time pain pathways are active in sickle cell patients.

Our group, using *PAINReportIt*® an electronic version of the McGill Pain Questionnaire[26] that allowed us to obtain not only the pain intensity and location of pain, but also its quality, and pattern, found that at a routine clinic visit, 66% of subjects reported having pain that day, and almost 92% chose verbal descriptors that are associated with

neuropathic pain The overall pain score in adult sickle cell patients was as severe as that in cancer patients. Interestingly, though this study was ongoing throughout the year, 18% felt that their pain on that day was caused by the weather.[1] Others have suggested in clinical case reports of peripheral neuropathy and neuropathic pain in those with sickle cell disease, but the reported clinical findings were inconsistent regarding diagnosis of neuropathic pain and presence of allodynia and hyperalgesia.[27]

According to the International Association for the Study of Pain, neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system either at the peripheral or central level.[28] Presence of allodynia and hyperalgesia are defining characteristics of neuropathic pain. Non-noxious thermal and mechanical stimuli that evoke pain in animal and human models or hyperalgesic responses to noxious thermal or mechanical stimuli are classic diagnostic indicators of neuropathic pain. Many investigators [29-35] have demonstrated the role for mechanical and thermal allodynia and hyperalgesia in animal models of neuropathic pain. As well, other classical neuropathic pain conditions[28] such as trigeminal neuralgia are noted for the profoundly painful effects of non-noxious stimuli as minor as a draft of air or light touch and hyperalgesia. Whereas cold atmosphere is a direct stimulus to trigger pathophysiologic response leading to cold allodynia and hyperalgesia (depending on actual temperature), windy conditions can be a source of a mechanical stimulus.

Consequences of the hypothesis and discussion

In summary, pain for most people with SCD starts very early in childhood, and continues throughout life. This persistent and often unrelieved pain results in altered processing within the nervous system, hence neuropathic pain. This type of neural plasticity is clinically exhibited by the development of pain in patients stimulated by changes in the weather such that patients develop thermal allodynia or hyperalgesia when exposed to cold temperature and cold wind. The latter may even have a component of mechanical allodynia. We can speculate that cold temperatures were associated with the admissions for the patient reported by Dr. Herrick in 1910. He had a CBC on December 26, 1904 (and admitted to the hospital close to that date); the same day the Chicago Daily Tribune reported “the usual winter increase in mortality has begun after three weeks of exceptionally low death rate.” The increase was attributed to “an increase of atmospheric impurity.”[36] Interestingly, the winter of 1904 was the tenth coldest in Chicago’s history.[37] Two years later, Dr. Herrick’s patient was again admitted:” the young man reported that he had been laid up in a hospital from Dec. 26, 1906, to Feb. 26, 1907.” The winter of 1907 was relatively balmy for Chicago, with an average temperature of 29 °F.[37]

We believe that efforts should be directed to further characterize neuropathic pain in SCD, and develop strategies to both prevent and better treat neuropathic pain in sickle cell disease. Then health care providers can offer better advice than to avoid the cold.

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