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Somnolence syndrome after cranial irradiation: a literature review

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Abstract Somnolence syndrome is a commonly seen, early-delayed side effect of radiation treatment to the brain. Despite being a recognised side effect for over 30 years, many associated aspects of the syndrome are still unclear, such as which patients are most prone to the condition, what are its associated symptoms, what is its aetiology, what treatment factors affect it and how can it be managed? Literature has shown that somnolence syndrome can occur in children and adults after receiving cranial irradiation. The syndrome is characterised by a variety of symptoms, including mild drowsiness to extreme exhaustion, low-grade fever, nausea, anorexia and headache. Symptoms generally appear between five to six weeks after the completion of treatment. Why and how the syndrome comes about is still uncertain. Popular theory suggests that it is due to transient demyelination of the nerve fibre. The condition has been shown to appear at doses as low as 12 Gy and up to 54 Gy with a fraction size dependence not yet established. The use of steroid therapy has proven to be an effective method to reduce the occurrence of somnolence syndrome in patients receiving cranial irradiation, with the optimal regime still to be determined. Health care professionals should acknowledge and warn their patients of the syndrome, ensuring proper care is available if it develops. Further study is required on the aetiology of the syndrome, the late neurological outcomes of the syndrome and the optimal steroid schedule for its management.

Keywords: cranial irradiation, radiation therapy side effects, somnolence syndrome

Introduction

Somnolence syndrome is an early-delayed side effect of radiation treatment to the brain, characterised by extreme lethargy in conjunction with signs of increased intracranial pressure (e.g., headache, nausea, vomiting and anorexia).[1] Despite being a recognised side effect for over thirty years,[2] many associated aspects of the syndrome are still unclear. These aspects include: identifying patients that are most prone to the condition, what are its associated symptoms, what is its aetiology, what treatment factors affect it and how can it be managed? The aim of this paper is to review the literature on somnolence syndrome in order to answer the above questions, so that health care professionals can better prepare susceptible patients for what is to come.

Method

The research carried out for this paper was done largely though electronic resources. Most articles were accessed through electronic databases, namely PubMed, Wiley InterScience, Scopus and Science Direct. When searching databases keywords were used such as; somnolence syndrome, cranial irradiation, radiation side effects, brain, prophylactic cranial irradiation. Three articles were accessed through hard copy at the Peter MacCallum Cancer Centre's Central Cancer Library, while another three were accessed through a document delivery service run by RMIT University. The data searches were not limited to a certain time period due to the lack of current articles and the small amount of literature on the topic.

Results

Presentation

Somnolence syndrome is characterised by a wide variety of symptoms. These range from mild drowsiness to extreme exhaustion, low-grade fever, nausea, anorexia and headache.[1] The condition was first documented by Druckmann in 1929, when treating children for ringworm of the scalp with 150kV x-ray.[2] Many of the children developed somnolence associated with anorexia, apathy, and headache. Since then, multiple studies have been dedicated to the topic, with all reporting similar symptoms.[2-4] Freeman, *et al.* (1973) noted that the most affected children could sleep for as long as 20 hours a day.[2]

Others have questioned whether increased sleep is actually a symptom. Faithful and Brada (1998) conducted a study where 19 patients who had received cranial irradiation were asked to keep a diary of how they were feeling and to scale certain symptoms.[5] They found that although patients experienced increased drowsiness, lethargy, clumsiness and slow mental processes, they did not require more sleep. Patients commented on the symptoms being 'a sensation that was mentally disabling and a disruption to physical activity by an overwhelming feeling of exhaustion' (p.253).[5] These results support results from an earlier study conducted by the same authors in which somnolence was described as a mental rather than physical feeling, and referred to the struggle of fulfilling everyday tasks as being frustrating.[6] These studies involved only adult patients, so it is possible that the clinical appearance of somnolence syndrome may vary between children and adults.

Time of presentation

The time of presentation and the duration of somnolence syndrome are fairly well documented in the literature.[1,2,4-9,12-14] Symptoms generally appear between five to six weeks after the completion of treatment.[2] However, they have been found to appear as early as four weeks[4] and as late as eight weeks.[7] The

duration of the syndrome has been found to be between two to 14 days, with a median of seven days.[4] Faithful and Brada (1998) however, found a slightly different, more distinctive pattern of occurrence.[5] Through the method of keeping a diary, they were able to monitor the patient's experience on a day-to-day basis and propose that two phases of the syndrome exist. They found that all patients in their study developed symptoms two weeks post-treatment completion. Symptoms then resolved only to resurface in the fifth week, lasting two to five days. Patients in this study were of a wide age group, had a variety of primary brain tumours with different dose and fractionation regimes.

The reason results like this have not been observed previously may be due to the fact that most previous studies on somnolence syndrome have been carried out retrospectively, with patients being questioned after the period of interest or at irregular intervals. All literature suggests that the syndrome disappears spontaneously and completely with patients returning to normal alertness and mental function with or without corticosteroid treatment.[1,2,4,7,8,12,14]

Incidence

Somnolence syndrome has generally become recognised as a condition affecting children with acute lymphocytic leukemia (ALL) after receiving prophylactic cranial irradiation.[2-4,12] However, studies have begun to find that somnolence does in fact appear in adults after irradiation for primary brain tumours.[5,6] Faithful and Brada (1998) found that 16 out of 19 patients, aged between 20 and 71, experienced somnolence after receiving cranial irradiation.[5] The authors of this study suggest that little information about somnolence syndrome in adults is available. This is due to health care professionals being particularly interested in developmental effects of cranial irradiation in children, and hence being more aware of its occurrence in a younger age group.[6]

Goldberg, *et al.* (1992) reported somnolence syndrome occurring in an adult patient following total body irradiation in preparation for a bone marrow transplant.[8] The 38-year-old patient experienced 40° C fevers, headaches, extreme lethargy and was found sleeping entire days, after receiving 13.2 Gy in six fractions over three days. It is suggested that lethargy is an expected outcome after bone marrow transplant and so radiation induced somnolence may often go unnoticed.[8] If somnolence is apparent for patients receiving total body irradiation, then the syndrome may in fact be a much more common condition in patients receiving cranial irradiation. This is particularly possible considering the aforementioned likelihood of its occurrence in adult patients.

Neurological side-effects

It has been suggested that despite earlier thinking, somnolence syndrome may be associated with late neurological side-effects.[14] Ch'ien, *et al.* (1998) evaluated 49 leukemic children undergoing prophylactic cranial irradiation, using electroencephalograms (EEGs) done before and at intervals during and after treatment.[14] Twenty-nine of the participants developed somnolence syndrome, with EEGs indicating marked slowing, often decreasing more than three standard deviations below the expected mean frequencies. Of these 29 children, seven went on to develop learning disabilities and seven developed seizure disorders. The children who did not experience the condition at all, showed no signs of long-term neurological toxicities. Further studies by the same authors questioned these results, indicating that at 3–4 years post treatment the cognitive function of children who experienced somnolence syndrome is comparable to that of children who did not develop the condition.[15] However Ch'ien, *et al.*[12] speculate on the conclusiveness of these latter results, advising that statistical data did not accurately represent the incidence of neurological outcomes and also that many disorders would not be present at such a short time after treatment. This highlights an area requiring further study.

Aetiology

The aetiology of somnolence syndrome is still uncertain. The most common theory in the literature states that somnolence syndrome arises due to radiation-induced transient demyelination of the nerve fibre.[1,9,10] This theory agrees with findings in an early study by Lampert and Davis (1964) who carried out autopsies on patients after receiving radiation therapy.[9] One patient, who presented three months after radiation treatment, with neuromuscular facial symptoms and who died a week later, was found to have 'punched-out plaques of demyelination within the field of radiation'.[9] Also, at autopsy, no residual carcinoma was detected signifying the damage was radiation induced. The authors suggest this is an extreme example of the early-delayed reaction of radiation on the brain.

This theory also explains the timing of the symptoms. It is suggested that radiation inhibits oligodendroglia from synthesising myelin.[10] The latent period before symptoms arise corresponds to the five to 10 week turnover time of myelin, with recovery occurring after increased myelin synthesis. Another theory on the syndrome is that it arises due to direct microvascular damage to the cell membranes, affecting both the oligodendroglial cells and the brain parenchyma,[11] however little research has gone into investigating this theory thoroughly.

Clinical presentation of somnolence syndrome has also been associated with an abnormal electroencephalogram (EEG).[2,3] Ch'ien, *et al.* (1980) found increased slowing on EEGs of children who experienced somnolence syndrome after cranial irradiation, compared to those without somnolence syndrome. This has been associated with a diffuse cerebral disturbance of the whole brain.[2]

Radiation therapy – dose

The effects of radiation dose have been investigated to determine the influence on somnolence syndrome. The impact of total dose on somnolence syndrome was discussed by Ochs, *et al.* (1991) after comparing outcomes in leukemic children receiving either 18 or 24 Gy prophylactic cranial radiation.[7] They found the incidence of somnolence syndrome to be similar in both groups with no significant difference seen in either. However, a decrease in severity of symptoms and a later presentation of symptoms was associated with the lower dose. This indicates that 18 Gy is the better option for prophylactic cranial irradiation in terms of decreasing the severity of side effects, especially considering that it has been found to be just as effective in preventing recurrence as 24 Gy (Nesbit, *et al.*, 1981[3]).

Miyahara, *et al.* (2000) reported a case of a 16-year-old boy who experienced somnolence syndrome six weeks after receiving 12 Gy total body irradiation in preparation for a bone marrow transplant.[13] This is the first study to describe the syndrome occurring at such a low dose, as all other studies have focussed on 18 or 24 Gy. This indicates that somnolence syndrome may in fact occur at lower cranial doses as well as in children receiving total body irradiation, highlighting the need for increased awareness of the condition.

Radiation therapy – fractionation

Fractionation size has also been explored to uncover whether it has an impact on somnolence syndrome. Littman, *et al.* (1984)

investigated the effect of reducing the fraction size on early-delayed toxicities.[3] Their study included 97 children receiving 18 Gy cranial irradiation, 31 of whom received 1 Gy fractions whilst 66 received 1.8 Gy. The data showed 'the same frequency and severity of the somnolence syndrome in the two groups, and thus failed to substantiate a definable fraction size dependence'.[3]

Faithful and Brada (1998) however, suggest that accelerated fractionation may influence the severity of somnolence syndrome.[5] Their study showed that the eleven patients treated with an accelerated fractionation schedule of 1.6 Gy bi-daily, experienced more severe somnolence and fatigue compared to the eight patients who received a conventional fractionation schedule of 1.8 Gy once daily. No significant differences were seen in the frequency or time of occurrence. The patients in the conventional fractionation arm of this study received varying doses and for different localised primary tumour sites. This may affect the validity of these data as too could the small sample size of patients.

Radiation therapy – area/volume

Questions have been raised on whether the area and/or volume of the brain irradiated have an affect on the incidence of somnolence syndrome. Generally, the condition was associated with irradiation of the whole brain,[1–3,12,13] however recent studies have shown that the syndrome may also appear after treatment to a localised area of the brain.[1,5] Kelsey & Marks (2006) report on a 29-year-old patient who received 54 Gy in 1.8 Gy fractions to a benign meningioma located in the pineal region of the brain.[1] Five weeks post treatment, the patient developed extreme fatigue, mild fevers and headaches. Treatment fields were conformed to the tumour, so areas of high dose were localised, however dose-volume histograms indicated that 50% of the entire brain received 10 Gy or more. The question lies in whether the somnolence syndrome was brought on by the limited region being irradiated to a high dose or by the larger area receiving a smaller dose.

Kelsey and Marks (2006) suggest that a possible aetiology for the syndrome may be the irradiation of the reticular activating system (RAS), which is a 'collection of neurons… responsible for arousal and sleep'.[1] The RAS is located proximally to the pineal region and was likely to receive a significant part of high dose. This may cause transient demyelination, inducing a temporary stage of somnolence. Further studies would be needed to confirm this hypothesis.

Faithful and Brada (1998) also show that somnolence syndrome occurs in patients receiving localised treatment for primary brain tumours.[5] Patients in their study were treated conformally for high grade glioma (n = 15), pituitary adenoma (n = 3) and medulloblastoma (n = 1). Sixteen of these 19 patients developed somnolence syndrome. Again it is uncertain whether this is caused by focal areas of high dose or large areas of lower dose, or whether one part of the brain is more prone in inducing somnolence syndrome. Little evidence exists on the topic and so no conclusion can be drawn.

Steroid treatment

The correlation of somnolence syndrome and the administration of steroids during and/or after cranial radiation therapy has been investigated. Steroids have long been used in conjunction with radiation therapy for their ability to reduce the toxicities associated with cerebral oedema.[12] Mandell, *et al.* (1989) conducted a pilot study to assess the occurrence of somnolence syndrome in leukemic children with varying tapering schedules of prednisone throughout radiation treatment.[12] Thirty-eight children received cranial irradiation of 18 Gy in 1.8 Gy fractions, beginning at specific times along the steroid tapering schedule. Thirty-two patients received ≥15 mg/m^2 of prednisone for the whole course of treatment, while only six received ≤15 mg/m^2. Five participants in total developed somnolence syndrome, four of which received doses ≤15 mg/m^2. This incidence of development (13%) is low compared to other studies, that report incidences between 58–79%.[2,3] This may be attributed to the majority of patients receiving ≥15mg/m of prednisone.

The same study also found that of seven patients who complained of headaches during the course of radiation treatment, five went on to develop somnolence syndrome, indicating a possible correlation between the two. Mandell, *et al*. (1989) concluded from their data that 'steroid coverage during cranial radiation significantly reduced the incidence of headaches and the somnolence syndrome'.[12] They recommend a minimum dose of 15 mg/m^2 to be given to children receiving prophylactic cranial irradiation for maximum benefit.

Uzal, *et al*. (1998) expanded on these findings and investigated the optimal dose of dexamethasone to reduce the incidence of somnolence syndrome.[4] Thirty-two leukemic children were randomised to receive 2 or 4 mg/m^2 of oral dexamethasone throughout the course of cranial irradiation and tapered in the five days following treatment completion. Of children in the low dose group, 64.3% developed somnolence syndrome, compared to 17.6% in the high dose group. This reiterates the findings of Mandell, *et al.* (1989) in that the management of somnolence syndrome is steroid dose dependent. Both of these studies highlight the benefit of steroids on children receiving cranial irradiation, however similar benefits have also been shown in cases of adults.[1,8]

The aforementioned case study of an adult meningioma patient discussed by Kelsey and Marks (2006) showed marked improvement of symptoms after administration of prednisone, with symptoms being completely resolved after one week.[1] Similarly the adult patient receiving total body irradiation discussed by Goldberg, *et al.* (1992) also responded well to steroid treatment following somnolent symptoms.[8] However, the authors of this latter study, highlight that caution must be taken when administering steroids to post-transplant patients, due to their increased risk of infection.

Quality of life

Somnolence syndrome can have a significant impact on the quality of life of a patient.[6] Faithful (1991) discussed thoroughly how little information is given to patients concerning what to expect after treatment, possibly due to the lack of awareness of the syndrome.[6] She found that often the occurrence of somnolence syndrome caused anxiety in patients, because many assumed it was a sign of disease recurrence. She also states that 'the unpredictability of the subjects' experience produced disruptions in their lives and themselves that went beyond the physical sensations of somnolence syndrome'.[6]

Whether more recognition is given to the syndrome today is hard to decipher from the literature, especially considering the lack of recent studies. However, the evidence highlights the importance of communicating to the patient the possibility of the syndrome occurring, to prevent unnecessary anxiety. In terms of children affected by the syndrome, little evidence discusses the impact it has on their lifestyle. From the wide range and variable severity of symptoms, it would be difficult to generalise a typical child's experience. However, it could be assumed that the most significant effect the condition could have on a child, would be on their learning capabilities in a school setting.

Recommendations

Aside from the possible medical aid available for the treatment of somnolence syndrome (i.e. steroid therapy), recommendations have been made for the social care of these patients. Faithful (1991) suggests more information should be given to patients about what to expect after treatment completion, to better prepare them if symptoms develop.[6] She also suggests that the time between follow-up appointments should be reduced so that symptoms can be discussed earlier if they present, and the patient can be reassured that it is not a result of treatment failure. An ideal time for follow-up appointments would be around five to six weeks post treatment, corresponding to the estimated time of its occurrence. In a later study, Faithful and Brada (1998) have recommended providing specialist nursing care and telephone support for patients and relatives for when symptoms present,[5] and modifying patient appointments to match the nature of the syndrome.[5] These suggestions were made in relation to adult patients experiencing somnolence syndrome, however they can also be carried over to include the parents of inflicted children.

Discussion

While the information found in this literature review is valuable and relevant, it is difficult to draw definite conclusions on many areas surrounding the topic. As commented on throughout this paper, this is largely due to the quality of the literature available. Little of the literature is current, making it difficult to make adequate correlations with current practice. Also, many of the studies did not have ideal research practices. Sample sizes were often quite small, reducing the validity of the data, while many of the articles were only case studies, discussing individual cases. There were also studies involving patients with a variety of brain disease, and treated with a variety of doses and techniques, again limiting ones ability to draw definite conclusions.

There are many areas surrounding the somnolence syndrome that require further study. For research to be of most use, significant sample sizes should be obtained, relevant testing parameters should be consistent such as, patients should be of a similar disease type or involving similar regions of the brain, similar doses should be given or similar techniques used. The method of research should be appropriate, taking into account the estimated time of occurrence of the syndrome. Tools such as patient diaries or questionnaires may be useful to track the exact behaviour of the condition over a certain time scale.

Conclusion

Somnolence syndrome is a common and significant early delayed side-effect of patients receiving cranial irradiation. As documented, its occurrence in both children and adults after cranial irradiation is significant, highlighting the need for greater recognition and management methods. Health care professionals should acknowledge and warn their patients of the syndrome and ensure proper care is available if it develops. Further study is required on the aetiology of the syndrome, the late neurological outcomes of the syndrome and the optimal steroid schedule for its management.

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