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Treatment of Infectious Mononucleosis with High Dose Vitamin D_3 in Three Cases

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Abstract

Infectious mononucleosis often results in significant morbidity and disability lasting up to six months. It is known that vitamin D induces cathelicidin production that can rapidly responds to some viral, bacterial and fungal infections. The Epstein Barr virus is able to block the vitamin D receptor thus blocking the ability to fight this infection. This article presents three cases, which responded quickly to loading doses of vitamin D (150,000-200,000 IU) followed by a month of 10,000IU daily.

Keywords: Infectious mononucleosis; Vitamin D; Epstein Barr virus

Introduction

This article reviews three cases in a single clinical practice of documented infectious mononucleosis treated with high dose vitamin D (50,000 units of vitamin D_3 used daily for 3-4 days, followed by 10,000IU for a month). All 3 patients were quite ill with worsening symptoms daily prior to the treatment with vitamin D_3, which resulted in significant improvement of symptoms and energy within days of treatment and complete resolution of symptoms in less than two weeks. Vitamin D is required for cathelicidin induction *via* the VDR and allows the innate immune system to quickly respond to some viral, bacterial and fungal infections [1]. As well, with new knowledge that proteins encoded by the Epstein Barr Virus (EBV) can block the Vitamin D Receptor (VDR) it would be prudent to replete vitamin D levels quickly. The immediate response is activated by the innate immune system, *via* the toll receptor for the induction of cathelicidin, which is vitamin D_3 dependent [2].

Background

Infectious Mononucleosis (IM) is a common debilitating illness in adolescents or young adults. Each year about 1-3% of all college students are affected [3]. There appears to be seasonality to IM, with a peak incidence at the end of winter and spring [4] when vitamin D levels are lowest. The symptoms of IM usually include fever, pharyngitis, headache, fatigue and sleepiness, splenomegaly, lymphocytosis with atypical lymphocytes, but can also mimic many other diseases. Neurologic complications are not uncommon acutely and there is evidence that EBV viral infections are a risk factor for future development of multiple sclerosis [5]. Vitamin D supplementation may mitigate EBV reactivation especially in the obese who are more prone to be deficient [6]. Of concern is that some lymphoproliferative disorders may be attributable to or induced by this infection. The only treatment at present is supportive therapy for IM at this time. The usual course in young adults is about 2-4 weeks with fatigue lasting for 6 weeks and in some individuals the symptoms last for 6 months or longer.

Case Presentation

Case 1

A 17-year-old female developed headache, fever, sore throat, lymphadenopathy, splenomegaly, periorbital edema, extreme fatigue, sleepiness and inability to concentrate at the end of March. She had been on 2000IU of vitamin D throughout the winter but her 25(OH) D levels may not have been high enough to protect her.

She was taken to her pediatrician who suspected a strep throat and Amoxil was prescribed. A couple of days later the symptoms were worse and she developed a rash typically seen when amoxil is used in a patient with IM. Her symptoms of fatigue, sleepiness and inability to concentrate had increased significantly. She revisited her pediatrician who suspected IM. A mono spot test and EBV studies were both positive. Treatment with 50,000IU vitamin D_3 was initiated for 3 days followed by 10,000IU daily for a month. Five days after starting the vitamin D she had significantly improvement in fatigue and concentration. Within 10 days she returned to her normal premorbid functioning with normal energy. Compliance using the 10,000IU following the loading dose was very good. Her 4-week post treatment vitamin D level was 204nmol/l.

Case 2

A 17-year-old male developed headache, fever, sore throat with significant lymphadenopathy, splenomegaly, significant difficulty swallowing, weight loss, fatigue and exhaustion, loss of concentration and sleepiness at the end of April. He had not taken any supplemental vitamin D during the winter months. He was seen by his physician who suspected mono and ordered testing which showed a positive mono spot test as well as positive EBV studies. Supportive therapy was recommended. With worsening symptoms and increasing fatigue, and difficulty swallowing, vitamin D_3 50,000IU was initiated for 4 days followed by 10,000IU daily for a month. Six days following treatment there was significant improvement in energy and concentration and he was able to return to school and his fatigue resolved in less than 2 weeks. His 4 week post treatment 25(OH)D level was 89nmol/l. On further questioning compliance following the loading dose was intermittent.

Case 3

A 16-year-old male developed headache, fever sore throat along with lymphadenopathy, difficulty swallowing, profound fatigue and exhaustion at the end of March. He had a vitamin D level done

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previously which was in the deficient range of 44nmol/l, but had not been supplementing as advised prior to the illness. Supportive therapy was recommended, and he was to take vitamin D_3 50,000IU for 4 days and then 10,000IU for a month and then reduce to 2000IU daily. His symptoms improved within a matter of days and he returned to school again without fatigue. The lymphadenopathy recovered quickly within 2 weeks by history. Compliance was very good following the loading dose. However, he continued on vitamin D 8-10,000 IU for 3 months and on re-measuring his vitamin D level it was at 338nmol/l. He was advised to reduce this to 2000IU.

Discussion

As in the case of these three patients, there is good evidence that 97% of people in this population have inadequate levels of vitamin D in late winter and spring [7]. Adolescents and young adults are even more likely to have low levels and most are deficient. Even minor insults or stressors to the body such as arthroplastic surgery to the knee may reduce vitamin D levels by 40% and levels do not recover quickly [8]. Infectious mononucleosis is a considerable stressor and causes significant inflammation and morbidity.

The question then becomes: how does one quickly and safely replete these individuals to help them recover? Using 4000IU daily raises levels by about 25nmol/l in three weeks which for an acute illness such as this may not be quick enough [9]. A single dose of vitamin D 100,000IU will raise 25(OH)D levels from 86.4 to 114.1 nmol/l in 1 week or a rise of about 20nmol/l [10]. This is similar to the option taken in these patients. There is no evidence that using 10,000IU of vitamin D on a daily basis for less than 6 months causes harm [11]. Another infectious disease (Tuberculosis) has been shown to respond to high dose 25(OH)D_3 at 10,000IU a day [12]. Lower doses have not shown this kind of response [1]. However, doses such as 500,000IU of vitamin D used once a year for osteoporosis have not been shown effective, may be harmful and should not be used [13]. The first patient had 25(OH)D levels seen in patients who have significant sun exposure and she recovered very quickly. The second patient had levels of 25(OH)D levels that were in the low normal range and thus his recovery was less rapid. The third patient recovered quickly but did not reduce his dose as instructed and had a significantly high level of 338nmol/l. None of these levels are considered toxic and they did not present with any symptoms suggestive of toxicity. The higher 25(OH)D levels in two of these patients were well within the accepted margin of safety (<375mnmol/l) or for the risk of hypercalcemia which occurs at levels >600nmol/l [11].

It has been suggested that MS and diseases associated with the EBV virus may be modulated by vitamin D status [14]. Another study has shown that mean 25(OH)D levels are significantly lower in IM patients and suggests the two major risk factors for autoimmune disease like MS may not be independent risk factors [15]. Environmental factors such as vitamin D may modulate MS risk [16]. Vitamin D is essential for the proper functioning of the immune system to fight off infections such as EBV, which is an encapsulated virus [1]. Since the VDR may be blocked from functioning by proteins encoded by the EBV [2] enough vitamin D must be present to restore function. Vitamin D can prevent EBV reactivation and Vitamin D is considered to have direct antiviral effects on envelop viruses [17]. With adequate vitamin D appropriate proteins like cathelicidins are encoded to rid the body of infection and prevent complications at the time of infection and in the future. Vitamin D_3 (high dose) has also been shown to reduce EBV nuclear antigen -1 in relapsing remitting MS [18].

There has been some advancement in prevention by trying to incorporate a vaccine for this illness. A Phase two clinical trial using a 3-dose regime recombinant EBV subunit glycoprotein 350/aluminum hydroxide vaccine for infectious mononucleosis has been found to be effective and seroconversion to this glycoprotein remained positive for >18 months [19]. However, this is not available commercially at this time.

Conclusion

These three patients present rapid recovery in IM, which often leads to a prolonged illness that takes from six weeks to six months to clear with a small percentage having a significantly longer illness. The use of a higher loading dose of vitamin D may represent an option and present a new paradigm for treatment of infections when the 25(OH)D levels need to be repleted quickly. It would be useful in shortening the effects of this devastating illness with its protracted morbidity and reduced risk of MS in the future. Early treatment may reduce morbidity substantially thus having a high index of suspicion, ordering lab work and making the diagnosis at the earliest time of infection may be warranted.

More studies are required to substantiate this link including studies looking at VDR polymorphism and assess viral clearing using this treatment.

Highlights for Review

- High dose vitamin D used as rapid repletion is safe.
- Vitamin D repletion may reduce inflammation, complications and length of illness in infectious mononucleosis.
- The prevention of future Multiple Sclerosis with this intervention is a possibility knowing the mechanism of immune dysfunction.

Ethical Approval

Ethical approval was not applied for in this clinical situation since treatment of these three individuals with rapid repletion of vitamin D is safe and commonly used in practice.

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