Schizophrenia and Vitamin D deficiency

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ABSTRACT

Vitamin D, a multipurpose steroid hormone, is vital to health. Vitamin D deficiency is present in approximately 30% to 50% of the general population. Its deficiency is now considered a worldwide pandemic. A strong correlation exists between vitamin D deficiency and the pathogenesis of several medical disorders. It is also being increasingly implicated in the pathology of several cognition and mental illness. Scientific data suggests that raising vitamin D levels to normal may help reduce the elevated morbidity and mortality risk associated with this deficiency. This study confirms a possible causal association between vitamin D deficiency and schizophrenia.

Keywords: schizophrenia, vitamin D, depression, mental illness

Abbreviations: CNS: Central nervous system; DSM: Diagnostic and Statistical Manual of Mental Disorders; D2: egrocalciferol; D3: Cholecalciferol; 25-OHD: 25-hydroxyvitamin D; SAD: Seasonal Affective Disorder

1. INTRODUCTION

Vitamin D refers to cholecalciferol and ergocalciferol, both biologically inactive precursors of this sunshine vitamin. Cholecalciferol or Vitamin D3, is produced photo-chemically in the skin after exposure to sunlight (Norman et al, 1998), while egrocalciferol or Vitamin D2 is produced exogenously and enters the circulation after gastrointestinal absorption from ingesting food such as fortified dairy products, fatty fish, and eggs (Ovesin et al, 2010). Vitamin D deficiency or insufficiency is prevalent in practically every segment of the U.S. population, including children and young adults (Dong Y, et al, 2010). This deficiency is now being reported from virtually all parts of the world, including sunny countries (van der Meer et al, 2006; Mashal 2001; Gannage-Yared et al, 2000; Rucker et al, 2002). A strong correlation exists between vitamin D deficiency and the patho-physiology of several medical conditions. Although traditionally associated with defects of bone and calcium metabolism (Lips, 2001), it has now become recognized as an important vitamin for good health. Besides neonatal tetany, rickets, osteomalacia and osteoporosis (Wagnor et al, 2008) its deficiency has recently been linked to several other diseases, including multiple sclerosis, Crohn's disease, lupus, rheumatoid arthritis, colorectal cancer, and chronic

lymphocytic leukemia (Ramagopalan et al, 2010), cancer (Lappe et al, 2007), diabetes (Baz-Hecht et al, 2010), active tuberculosis (Nnoaham et al, 2007) and periodontal disease (Amano et al, 2009). Adequate levels of Vitamin D are also necessary for optimal cardiovascular health (Lee et al, 2008; Wang et al, 2008; Kim et al, 2008), with its deficiency being associated with hypertension (Kristal-Boneh et al, 1997; Forman et al, 2007), stroke (Pilz et al, 2008), heart failure (Pilz et al, 2008), cardiac arrhythmias (Chavan et al, 2007), coronary artery disease (Watson et al, 1997), and myocardial infarction (Giovannucci et al, 2008). Its deficiency has also been linked to excess cardiovascular mortality (Dobnig et al, 2008) and an increase in general mortality (Vacek et al, 2012). Recently, increasing evidence has linked vitamin deficiency with several psychiatric and neurological conditions like depression and Alzhiemer's disease (Lu'o'ng et al, 2011; Howland, 2011). The role of nutritional deficiencies, especially vitamin D deficiency in the patho-physiology of schizophrenia is also emerging (McGrath et al, 2011) Neonates born in the winter and those with hypovitaminosis D levels exhibit a higher propensity to develop schizophrenia (McGrath et al, 2010) Adult schizophrenics appear to have lower vitamin D levels (Itzhaky et al, 2012) This study was done to assess the prevalence of vitamin D deficiency in institutionalized patients with schizophrenia.

2. METHODS

We retrospectively reviewed the vitamin D results on all schizophrenic patients seen in our office during a period of six months. All patients were diagnosed to be suffering from schizophrenia by psychiatrists according to the criteria established by the revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 2000) All patients met the three diagnostic criteria: A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated): (1) delusions, (2) hallucinations, (3) disorganized speech (e.g., frequent derailment or incoherence), (4) grossly disorganized or catatonic behavior, (5) negative symptoms, i.e., affective flattening, alogia, or avolition. B. Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement). C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g. odd beliefs, unusual perceptual experiences) (DSM-IV, 2000) All patients were regularly seen by their psychiatrists and were stable on anti-psychotic medications. Vitamin D was measured as 25-hydroxyvitamin D in the blood. The levels were analyzed by chemi-luminescent immunoassay and reported as ng/ml. Although some previous studies had established 27 nmol/l as the lower limit of the normal range (Fraser, 1983), the accepted lower limit is usually accepted to be 30 nmol/l (Zeghund et al, 1997) Most laboratories define the normal range of vitamin D as being 30 to 74 ng/mL. In our study the levels were recorded and classified as follows: more than 30 ng/ml: normal; 21 to 30 ng/ml: mild deficiency; 11 to 20 ng/mL: moderate deficiency; 10 ng/ml or less: severe deficiency (Norman et al, 2007).

3. RESULTS

Of the total of 83 patients with schizophrenia, 63 had vitamin D levels measured. Of these, 46 (73%) had low Vitamin D levels(less than 30 ng/ml), while 17 (27%) had normal vitamin D levels (more than 30 ng/ml). Of the 26 females, 20 (77%) had low vitamin d levels and of the 37 males, 26 (70%) had low vitamin D levels. 10 of the 63 had severe deficiency (10 ng/ml or less), 22 of the 63 had moderate deficiency (11 to 20 ng/mL) while 14 of the 63 had mild deficiency (21 to 30 ng/ml). No difference was noted between the males and females.

4. DISCUSSION

Vitamin D receptors and vitamin D metabolizing enzymes are present throughout the brain. Vitamin D affects numerous neurotransmitters and neurotrophic factors in mental disorders (Humble et al, 2010) It protects the brain preventing vascular injury through antioxidant and anti-inflammatory mechanisms (Cass et al, 2006; Baksi et al, 1982; Harms et al, 2008; Berk et al, 2008; Stumpf et al, 1987; Stumpf et al, 1995; Wion et al, 1991; Watson et al, 2002; Partonen, 1998). Its deficiency is associated with negative CNS effects in animal studies, including increased anxiety, decreased activity, and muscular and motor impairments (McCann et al, 2008).

4.1. Role of Vitamin D in schizophrenia

Schizophrenia is a worldwide disease, with a prevalence of approximately 1% (Bhugra 2005). It is the third leading cause of global disability in persons aged 15-44 years. It is responsible for 2.8 percent of the global burden of disability (Health Organization, 2001). The clinical features and management of schizophrenia has been well studied (APA, 2000; Sullivan et al, 2003; Woo et al, 2004). These patients suffer from multiple co-morbid psychiatric (Foti et al, 2010; Palmer et al, 2005) and medical conditions, including pulmonary, cardiovascular and endocrine diseases (Jeste et al, 1996; Casey et al, 2011; Goff et al, 2005; Copeland et al, 2007). They also appear to get suboptimal medical care (Brown et al, 2000; Felker et al, 1996). Institutionalized patients with schizophrenic may be subject to poor living conditions, poor diet, excessive smoking and alcohol intake, lack of exercise and reduced exposure to the sun (Wildgust et al, 2010). In general, patients with schizophrenia have a two to three fold higher mortality rate when compared to the general population (Laursen et al, 2007; Saha et al, 2007; Brown et al, 2010) and a reduction of 10-25 years in life expectancy. The role of vitamin D deficiency in this population is rapidly emerging and is being subject to clinical investigation (McGrath et al, 2011) Neonates born with hypo-vitaminosis D levels exhibit a higher propensity to develop schizophrenia (McGrath et al, 2010) Vitamin D levels are lower during winter and spring months and neonates born during this period have a significantly increased risk of later developing schizophrenia (Moskovitz, 1978; Torrey et al, 1997) Similar associations between schizophrenia and people living at higher altitudes with lower exposure to sunlight have been documented (Saha et al, 2006) Dark skinned migrants also appear to develop more schizophrenia, compared to white skinned migrants from the same regions (Cantor-Graae et al, 2005) Several studies have demonstrated that adult schizophrenics have lower vitamin D levels (Itzhaky et al, 2012) compared to the general population. The exact etiology is not known. Low vitamin D may alter gene expression and nervous system development (Mackay-Sim et al, 2004) Environmental factors also appear to play a role (Holick, 1995).

4.2. Role of vitamin D in psychiatric conditions

Vitamin D deficiency is associated with mood disorders, including seasonal affective disorder (SAD) (Thys-Jacobs et al, 1995; Wilkins et al, 2006; Glothe et al, 1999). Broad spectrum phototherapy appears to improve symptoms in SAD (Gloth et al, 1999). A high percentage of psychiatric inpatients (McCue et al, 2012; Berk et al, 2008) and outpatients (Humble et al, 2010) are deficient in vitamin D. Patients with higher levels of depressive symptoms or with depression often have vitamin D deficiency (Howland, 2011; Witte et al, 2008; Bertone-Johnson, 2009). Hypo-vitaminosis D has also been associated with bipolar disorders (Gracious et al, 2012) and psychosis (Berg et al, 2010). It has been incriminated in some neurological disorders, including Alzheimer's disease (Eyles et al, 2012; Pogge et al, 2010; Luong et al, 2011). Patients with Parkinsons disease also appear to by vitamin D deficient (L Ng K et al, 2012; Vinh et al, 2012).

4.3. Causes of Vitamin D deficiency

Vitamin D deficiency usually results from a multitude of factors, including dark skin, avoidance of sun exposure or living above and below latitudes of approximately 40° N and 40° S, respectively, or poor exposure due to religious reasons or being institutionalized. Vitamin D deficiency may also occur in infants, adolescents and pregnant and lactating women, primarily due to increased needs (Gultekin et al, 1987; Prentice, 1998). Obese individuals tend to deposit vitamin D3 from cutaneous and dietary sources in the body fat compartments, leading to reduced bioavailability (Wortsmanet al, 2000). Patients suffering from fat malabsorption syndromes, inflammatory bowel disease (Lo et al, 1985) and those with obesity related gastric bypass surgery may become vitamin D deficient (Compher et al, 2008; Reid, 1998) Certain medications can interfere with vitamin D absorption or metabolism, including orlistat, cholestyramine (McDuffie et al, 2002; Compston et al, 1978) corticosteroids and epilepsy drugs (Buckley et al, 1996; Goughet al, 1986). In vitro studies suggest that antipsychotic drug treatment may also lead to deficiency by inhibiting vitamin D synthesis (Lauth et al, 2010).

4.4. Prevention of vitamin D deficiency

Replacing vitamin D is generally cheap and easy. It is estimated that approximately 30 minutes of direct skin exposure of the arms and face to sunlight can provide all the daily vitamin D needs of the body (Holick, 1994) Fatty fish, such as salmon, mackerel, herring and sardines are the richest natural sources of vitamin D and an important way to maintain optimal levels (Nakamura et al, 2000) Fortified foods can also help supplement its intake such as fruit juices, grains, milk, cereal and oils with calcium and vitamin D (Calvo et al, 2004) Vitamin D is also available over the counter as a supplement or can be obtained in higher strengths with a doctor's prescription. Vitamin D toxicity is extremely rare. Prolonged massive doses may result in hyper-calcemia. Symptoms of toxicity may include anorexia, nausea, vomiting, weight loss, constipation and weakness (Hathcock et al, 2007). Toxicity may rarely cause confusion and cardiac arrhythmias (Favus et al, 1996).

5. CONCLUSION

It is estimated that as much as 60% of the adult US population suffers from vitamin D deficiency. Our population of institutionalized schizophrenia patients had a 73% incidence of hypo-vitaminosis D. This deficiency may contribute to the higher morbidity and mortality noted in this population. Psychiatric in-patients may be particularly vulnerable to vitamin D deficiency because of lack of exposure to sunlight, poor dietary habits, anticonvulsants therapy and overrepresentation of ethnic groups known to be at a greater risk. Consideration should therefore be given to supplemental vitamin D in these patients. A Finnish cohort supplemented with prenatal and infant vitamin D demonstrated a reduced adult risk for schizophrenia (McGrath et al, 2004) Obesity related depression shows an improvement with vitamin D supplementation (Jorde et al, 2008). There is growing evidence that supplementation in adults improves symptoms (Hogberg et al, 2012) in a variety of psychiatric disorders, including schizophrenia.

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Data and materials availability:

All data associated with this study are present in the paper.

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