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Vitamin D deficiency in first episode psychosis: A case–control study

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ABSTRACT

Background: Vitamin D deficiency is seen in a high proportion of people with established psychotic disorders, but it is not known if this is present at onset of the illness. We set out to examine vitamin D levels in people with their first episode of psychosis (FEP).
Method: We conducted a matched case–control study to examine vitamin D levels and rates of vitamin D deficiency in sixty nine patients presenting with their FEP and sixty nine controls matched for age, sex and ethnicity. Differences between groups were tested using student's-t tests, paired t-tests and odds ratios for further analysis.
Results: Vitamin D levels were significantly lower in cases than in controls ($p < 0.001$). The odds ratio of being vitamin D deficient was 2.99 in the FEP group relative to the control group. There was no correlation between vitamin D levels and length of hospitalisation in the patient group ($r = -0.027$, $p = 0.827$).
Conclusions: We found higher rates of vitamin D deficiency in people with FEP compared to matched controls. Given that vitamin D is neuroprotective; that developmental vitamin D deficiency may be a risk factor for psychosis, and that incipient psychosis may affect lifestyle factors and diet, future studies are required to examine this association further. In the meantime, there is a need for more widespread testing of vitamin D levels in FEP and for the development of appropriate management strategies.

1. Introduction

Low levels of vitamin D have traditionally been associated with musculoskeletal consequences (Wharton and Bishop, 2003; Boonen et al., 2006). In recent years, however, the importance of this essential nutrient across a range of conditions has become apparent. It is increasingly recognised, for example, that low vitamin D levels are seen in cardiovascular disease (Wang et al., 2008), diabetes (Holick, 2008) and multiple sclerosis (Orton et al., 2011) (Wood, 2012) and influence the body's ability to mount immune responses (Hewison, 2011).

Vitamin D levels in the general population are higher in men than in women and decrease with increasing age (Zadshir et al., 2005). There is also a relationship between low vitamin D levels and obesity (Wortsman et al., 2000; Vimaleswaran et al., 2013) and with smoking (Brot et al., 1999; Cutillas-Marco et al., 2012). It has been postulated that those with increased adipose tissue stores (in which vitamin D, being fat soluble, is stored), due to obesity, have lower circulating levels of vitamin D due to this increased storage capacity (Wortsman et al., 2000). Cigarette smoking has been associated with altered vitamin D metabolism, with increased hepatic cytochrome enzyme activity (Hermann et al., 2000) suggested as the mechanism of deranged vitamin D metabolism.

In humans, skin exposure to ultraviolet B sunlight is the major primary source of vitamin D (Holick, 2004), with diet contributing a maximum of 20% (Fuller and Casparian, 2001). Vitamin D levels thus vary seasonally, with levels in late winter and early spring around half of those in the autumn reflecting ambient levels of sunlight (Hypponen and Power, 2007). People with more pigmented skin need more sunlight to produce vitamin D, so are particularly affected by limited sun exposure, with lower levels of vitamin D consistently observed in Black and Asian populations (Ford et al., 2006; Looker et al., 2008; Mithal et al., 2009).

Vitamin D is involved in a number of brain processes including neurodevelopment, neurotransmitter expression, neurotrophic and

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growth factor regulation and is thought to be neuroprotective (Eyles et al., 2013). There is a growing interest in the relationship between vitamin D and mental health (Berk et al., 2008; Berg et al., 2010; Menkes et al., 2012) and it has been proposed that developmental deficiency of vitamin D may contribute to the aetiology of schizophrenia (McGrath, 1999; McGrath et al., 2004, 2010b).

All previous reports of vitamin D deficiency in psychosis have been in those with established disorder, and therefore could be due to prolonged hospitalisation, poor nutrition, or to the prescription of anticonvulsant medications (Pack et al., 2004). To our knowledge, no data exists on vitamin D levels at first onset of the disorder. We therefore tested the hypothesis that vitamin D levels in patients with their first episode of psychosis (FEP) are lower than those in their peers in the general population.

2. Method

The study population comprised 69 adults with a first episode of psychosis. All participants met the ICD-10 criteria for psychosis (codes F20-29 and F30-33) and had been admitted to psychiatric inpatient units in London and South-East England. Participants provided written informed consent. The project was approved by the Research Ethics Committee of The Joint South London and Maudsley and The Institute of Psychiatry NHS Research Ethics Committee.

The patients were matched for gender, age (plus or minus 5 years) and self-reported ethnicity (white, black or other), to 69 healthy controls from the same local population, recruited by means of internet and newspaper advertisements, and distribution of leaflets at train stations, shops and job centres. Those who agreed to participate as controls were administered with the Psychosis Screening Questionnaire (Bebbington and Nayani, 1995) and excluded if they met the criteria for a psychotic disorder or reported a previous diagnosis of psychotic illness. Additional exclusion criteria for both the control group and the cases were; a diagnosis of intellectual disability, terminal cancer, end-stage renal failure and pregnancy.

Vitamin D levels (serum 25-hydroxyvitamin D (25 OHD)) were determined by chemiluminescence immunoassay (DiaSorin, S.P.A. Saluggia (Vercelli), Italy). Vitamin D insufficiency was defined as 25 OHD levels between 25 and 50 nmol/L and vitamin D deficiency defined as levels below 25 nmol/L (Pearce and Cheetham, 2010).

Statistical analysis was performed using the Statistical Package for Social Sciences 18.0 for Windows (SPSS Inc., Chicago, Illinois, and USA). Data analysis was performed using correlation coefficients, student's-t tests, paired sample t-tests and analysis of variance (ANOVA) for parametric data where appropriate. An analysis of variance (ANOVA) was conducted to assess for significant differences between mean levels of serum vitamin D levels within groups. Post hoc analyses using the Scheffe post hoc criterion for significance was conducted where ANOVA demonstrated significant differences between the group means. Associations between vitamin D deficiency and the seasonal timing of the vitamin D measurement, and case–control status are expressed as odds ratios. All statistical tests were two-sided and the α-level for statistical significance was 0.05.

3. Results

The mean age of the cases was 31.0, (SD = 10.9; range 18–58); and of controls 30.7, (SD = 11.1; range 18–59). Twenty seven participants (39%) in each group were male. Within each group, 39 subjects were white (56%), 20 were black (29%) and 10 of Asian ethnicity (14%).

Mean serum vitamin D level was significantly lower in cases (36.5 nmol/L (SD = 23.0)) than in controls (53.8 nmol/L (SD = 33.0)) ($t = -4.064$, df = 68, $p < 0.001$). Vitamin D deficiency was present in 36.2% (n = 25) of cases and 15.9% (n = 11) of controls. Vitamin D sufficiency was found in 24.8% (n = 17) of cases and 41.1% (n = 31) of controls. The odds ratio of having vitamin D deficiency was 2.99 times higher in cases than in controls (OR = 2.99 (95% CI = 1.33–6.74); p = 0.008).

Significant differences in mean levels of vitamin D were found between ethnic groups among both cases ($F = 9.293$, df = 2, $p < 0.001$) and controls ($F = 8.777$, df = 2, $p < 0.001$) (Table 1). Vitamin D levels were significantly less in first episode patients of both white and black ethnicity than when compared to matched controls (Table 2). There was a lack of significant difference between the mean vitamin D level in cases and controls among the Asian sub-group ($t = -1.965$, df = 9, p = 0.081). The majority of this group was of Indian ethnicity (n = 8).

There was no effect of obesity (body mass index (BMI) > 30 kg/m^2) on vitamin D levels in the FEP group. The ten patients with a BMI of >30 had mean vitamin D levels of 49.3 nmol/L, (SD = 38.1) while non-obese patients (n = 43) had mean levels of 37.3 nmol/L, (SD = 20.1) ($t = 1.415$, df = 51, p = 0.163). Nor was there a difference in mean vitamin D levels in smokers (n = 34, mean vitamin D = 36.9 nmol/L, SD = 17.06) compared to non-smokers (n = 12; mean = 53.3 nmol/L, SD = 39.01) ($t = 1.998$, df = 44, p = 0.052). Data relating to BMI and smoking were not available for controls.

There was no evidence of an effect of anti-psychotics or anticonvulsant medication on vitamin D levels. Only four patients were prescribed anticonvulsants, one of whom was vitamin D deficient and two insufficient (mean = 30.95 nmol/L, SD = 10.52), reflecting the overall pattern of vitamin D levels among those not treated with anticonvulsant medication within the cases (mean = 36.85 nmol/L, SD = 23.57) ($t = -0.494$, df = 67, p = 0.623). Nor was there any difference in mean vitamin D levels in the 86% of cases, who were treated with antipsychotic medication (median duration 2 weeks (range 1–26 weeks)) (n = 56) (mean vitamin D = 37.09 nmol/L, SD = 18.60) and those who were not (n = 13) (mean vitamin D = 34.02 nmol/L, SD = 24.03) ($t = -4.32$, df = 67, p = 0.667). The mean vitamin D level in those cases treated with SSRIs (n = 17) was 46.33 nmol/L (SD = 30.66) which was significantly higher than in those with no SSRI use (n = 52; mean vitamin D = 33.30 nmol/L, SD = 19.20, $t = -2.075$, df = 67, p = 0.042).

Thirty nine percent (n = 27) of the FEP group and 48% (n = 33) of controls had blood sampling performed in the winter or spring (OR = 1.426 (95% CI = 0.725–2.803); p = 0.304). There were trends toward higher vitamin D levels in summer/autumn than in winter/spring within both groups (Table 3).

The median duration of time as an inpatient in the FEP group prior to blood sampling was 20 days (range 0–85 days). There was no correlation between serum vitamin D levels in the cases and their duration of hospital inpatient stay ($r = -0.027$, p = 0.827).

4. Discussion

This study shows for the first time that vitamin D levels are low at the onset of a first psychotic episode. In our sample, one third of people were vitamin D deficient at the time of their first episode of illness. The

Table 1
Differences in mean vitamin D levels within ethnic groups in case and control groups.

Ethnicity	Mean vitamin D levels (nmol/L) ± SD			F	DF	p-Value[a]
Cases	White (n = 38)	Black (n = 17)	Asian (n = 10)	9.293	2	<0.001*
	46.3 ± 25.4	22.6 ± 9.9[1]	25.1 ± 14.2[2]			
Controls	White (n = 38)	Black (n = 17)	Asian (n = 10)	8.777	2	<0.001*
	66.1 ± 36	32.6 ± 14.1[3]	39.2 ± 19.7[4]			

Difference in mean vitamin D levels among ethnic groups in comparison to white subgroup:
* < 0.05.
[a] Chi squared test.
[1] Mean difference (MD) = 21.64 nmol/L, Standard error (SE) = 5.67, p = 0.001.
[2] MD = 20.67 nmol/L, SE = 7.34, p = 0.024.
[3] MD = 31.22 nmol/L, SE = 8.21, p < 0.001.
[4] MD = 27.62 nmol/L, SE = 10.58, p = 0.039.