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Effects of Vitamin D Use on Outcomes of Psychotic Symptoms in Alzheimer's disease Patients

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Abstract

Objective: To identify medications which may prevent psychosis in Alzheimer's disease (AD) patients.

Methods: We compared the frequency of medication usage among AD patients with or without psychosis symptoms (AD+P vs. AD-P). We also conducted survival analysis on time to psychosis for AD patients to identify drugs with beneficial effects. We further explored the potential molecular mechanisms of identified drugs by gene signature analysis. Specifically, the gene expression profiles induced by the identified drug(s) were collected to derive a list of most perturbed genes. These genes were further analyzed by the associations of their genetic variations with AD or psychosis-related phenotypes.

Results: Vitamin D was used more often in AD-P patients than in AD+P patients. Vitamin D was also significantly associated with delayed time to psychosis. AD and/or psychosis-related genes were enriched in the list of genes most perturbed by Vitamin D, specifically genes involved in the regulation of calcium signaling downstream of the Vitamin D receptor.

Conclusion: Vitamin D was associated with delayed onset of psychotic symptoms in AD patients. Its mechanisms of action provide a novel direction for development of drugs to prevent or

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treat psychosis in AD. In addition, genetic variations in Vitamin D-regulated genes may provide a biomarker signature to identify a subpopulation of patients who can benefit from Vitamin D treatment.

Keywords

Alzheimer's Disease; Cognitive Decline; Vitamin D; Psychosis Symptoms; Systems Pharmacology; Clinical Data-Mining

1. Introduction

AD is the most common form of dementia (estimated to be 50−60% of all cases) and the sixth most common cause of death in the U.S. with the absolute numbers growing (1) though its prevalence is decreasing (2). Today, only five drugs approved by the U.S. Food and Drug Administration (FDA) are used to treat the cognitive dysfunction of AD, e.g. tacrine, donepezil, rivastigmine, galantamine, and memantine. These drugs are modestly efficacious for cognitive abilities in early to moderate stages of AD (3). However, none of them can stop or reverse the progression of this disease (3). As such, there remains a great demand for design and discovery of new medications or repurposing drugs that alter the course of AD. Our question is, can we find clues for AD treatment from the analysis of medication history of AD patients? The rationale for this approach arose from the fact that AD can co-occur with other diseases, and as such, multidrug therapy is common among AD patients. The substantial overlap between diseases in their risk factors points to the possibility of treating two relevant diseases with the same drugs.

In this study, we compared the medication history of two groups of AD populations, AD patients with or without psychotic symptoms (AD+P / AD-P), where psychotic symptoms include hallucinations and delusions. AD+P patients represent a subgroup with poor outcomes: more rapid cognitive and functional decline (4–7); higher rates of aggression (8); worse overall health (9); and shorter time to placement in a nursing home (7, 10), when compared to AD-P patients (11, 12). Our hypothesis is that a drug may have beneficial effects on AD patients if it is used more often in AD-P than in the AD+P population, because AD-P is a relatively positive outcome.

To explore the potential molecular mechanisms, other than the direct target(s) of an identified AD-beneficial drug, gene signature analysis can provide useful clues. Both disease and medications can alter gene expression patterns. It has been increasingly appreciated that such perturbations result in a specific transcriptome 'signature': i.e. a set of genes with a defined pattern of expression (13). Computational efforts have increasingly assembled and compared these signatures genome-wide, revealing unexpected drug–disease 'connections' when signatures correspond. If the transcriptome signature of a drug is negatively correlated with the disease signature, the drug might be able to reverse the disease transcriptome alterations, and hence, the disease phenotype itself. This approach has increasingly led to successful discoveries(13–16). For example, ursolic acid was identified as an inhibitor of fasting-induced muscle atrophy by gene-signature comparison(17). In the randomized, double-blinded, and placebo-controlled trial, right-handgrip strength of female subjects in

the ursolic acid group was found to be significantly better than that of subjects in the control group, though no differences were found in the other outcomes(18). The application of this approach on repurposing drugs for AD treatment has also been reported (19). Thus, the objective of this study was to identify medication use associated with altered risk for psychosis in AD, and to perform gene signature analysis in an effort to identify potential pathways for modifying AD+P risk.

2. Methods

2.1. Subjects

Subject ascertainment and characterization were previously described in detail (11). In brief, all subjects were participants in the University of Pittsburgh ADRC, seen between May 2000 and August 2014. Subjects were included if they had an initial primary diagnosis of Mild Cognitive Impairment (MCI) (20, 21) or Probable or Possible AD (22) after a clinical diagnostic evaluation consisting of a baseline neurological, neuropsychological and psychiatric evaluation, laboratory studies, and brain imaging with annual re-evaluation of neurological presentation, behavioral symptoms, cognitive tests, and functioning (23–26). Initial and annual visits included the Mini-mental State Examination (MMSE)(27). Telephone assessments were conducted at approximately six-month intervals between annual in-person visits, and they were also conducted at the time of annual assessment for individuals unable to return to clinic. All subjects were required to have an age of onset of cognitive problems starting ≥60 years old and no current or prior psychosis, including no prior personal history of a primary psychotic disorder (e.g. schizophrenia).

Psychosis was assessed at visits and by telephone using the Consortium to Establish a Registry for Alzheimer Disease Behavioral Rating Scale (BRS) which was administered to an informant knowledgeable about the patients' symptoms. The informant's relationship to the participant (available for 97.8%) and frequency of contact (available for 90.9%) was recorded. Informants were predominantly a spouse (55%) or an adult child (38%). 83% had contact (5 or more days/week with the participant; 63% lived with the participant.

Patients were classified as psychotic if they had one or more of BRS items #33–45 rated as present at least three to eight days in the past month: delusional misidentification of people, self or objects; paranoia, beliefs of abandonment or infidelity; believing someone is an imposter, belief that characters on television are real; belief that there are people in or around house that aren't there, belief that a dead person is still alive, belief that their house is not their home, auditory hallucinations, visual hallucinations. Symptoms were not rated if they occurred during an episode of delirium, were medication induced, or if the symptoms were hypnopompic or hypnogogic. AD-P was defined as the absence of all psychosis symptoms at all assessments.

All procedures were conducted under the research protocol approved by the University of Pittsburgh Institutional Review Board, and informed consent was obtained from subjects and/or their proxy.

2.2. Medication information

Information on all medications used by participants was collected at initial and annual visits, and during telephone evaluations. For AD+P patients, we only considered their medication usage from the date of the study entry to the first time of psychosis onset. For AD-P patients we considered all the available medication usage on and after the date of study entry. We selected the top 100 most used drugs for this analysis.

2.3. Statistical analysis

Chi-square test was performed to assess the association between psychosis and ever or never taking of each of the 100 candidate drugs during the follow-up. Log rank test was performed to test the difference in time to psychosis from time to entry of the study between patients who have ever or never taken each of the 100 candidate drugs during the follow-up. To adjust for multiple testing, Benjamini & Hochberg method (28) was used to control for the false discovery rate (FDR). For those drugs statistically significantly associated with time to psychosis with FDR ≤ 0.1, we also performed a multivariable Cox regression with baseline MMSE, baseline age, sex, race, and education, as covariates. We used the cox.zph function of R package survival to test the proportional hazard assumption (29).

The study data was maintained and managed using SPSS for Windows (v12–v15); the analyses were carried out using SAS (SAS Institute, Cary, North Carolina). $p<0.05$ was used as the threshold for statistical significance for all analyses except where stated otherwise.

2.4. Analysis of gene signatures induced by drugs

To understand the molecular mechanism behind the beneficial effects on AD, we analyzed the gene expression profiles induced by those drugs identified in the above analyses as significantly associated with occurrence and time to occurrence of psychosis. Differentially expressed genes (DEGs) induced by drugs were collected from commercial software Illumina BaseSpace (formerly Nextbio™) software (Santa Clara, CA, USA, http://www.nextbio.com). In BaseSpace, most of the raw gene expression datasets were from the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/) and the Connectivity Map database (CMAP) (13). Only genes with p values <0.05 and absolute fold changes >1.2 were considered as DEGs. All the DEGs induced by a drug can be considered as a gene signature for this drug. The drug-induced gene expression datasets were selected by searching with drug names and were refined by only keeping datasets of one single drug treatment vs. control. All the qualified gene signatures for an individual drug were analyzed by the meta-analysis engine implemented in the BaseSpace database to generate a list of persistent genes from multiple instances of similar perturbations. All BaseSpace analyses were performed utilizing the default parameters.

2.5. Effect of drugs identified above on cognitive decline

To test for the effects of drugs identified above on the rate of decline in cognitive function, measured by MMSE, we applied a mixed-effect model with random intercept and random slope. We assessed the interaction term between treatment group and time controlling for the baseline MMSE, baseline age, race, sex, education and use of drugs identified above.

3. Results

3.1 Characteristics of subjects

The characteristics of the subjects are shown on Table 1. The subjects who developed psychosis symptoms had lower baseline MMSE, generally took fewer numbers of drugs and had lower education levels.

3.2 Vitamin D is identified as a drug with more frequent use in AD-P patients and which is associated with delayed onset of psychosis symptoms.

Of the 100 drugs analyzed (Table S1), only Vitamin D (Ergocalciferol) showed a significantly higher frequency of use among AD-P subjects compared to AD+P cases with q-value <0.001 (Table 2). Detailed Chi-square test results on the 100 drugs can be found in Table S2. We then analyzed the association between all 100 drugs and time to psychosis, identifying 6 drugs, including Vitamin D, with significant associations (Table S3; multivitamin, Vitamin D (ergocalciferol), memantine, warfarin, ferrous sulfate, and omeprazole). These six drugs were significantly associated with a delay to psychosis onset, as determined by Cox regression (Table 3).

3.3 Genes induced by Vitamin D are enriched in association with AD and psychosis diseases

We focused our studies of gene expression on Vitamin D, as it was the only common drug in the above analyses of association with presence of psychosis and time to psychosis occurrence. We identified 47 biosets of gene expression profiles from GEO and CMAP 2.0 database as shown in Table S4. These biosets were from single exposures of different cell types to Vitamin D, with different exposure durations. They were subjected to meta-analysis to derive a list of most perturbed genes (defined as having significant changes in 20 or more of the 47 biosets). As shown in Table 4, fifteen genes were found as the ones most perturbed by Vitamin D. These 15 genes are direct transcriptional targets of Vitamin D receptor (VDR) (30–38) except ACVRL1 and FOSL2. However, FOSL2 was reported to bind with the VDR promotor to regulate VDR gene expression (39). We then searched the GWAS CatLog (https://www.ebi.ac.uk/gwas/) to find associations of variations in these genes with AD- or psychosis-related phenotypes. Multiple variants in EFTUD1 have been associated with cognitive ability (40), intelligence (41), and educational attainment (42). Variation in EFTUD1 has also been associated with left superior temporal gyrus thickness in schizophrenia patients (43). SNPs in CLMN are associated with the cognitive decline in AD patients (44) and response to treatment of the antipsychotic drug perphenazine (45), an antagonist of dopamine D1 and D2 receptors. An SNP in SERPINB1 is associated with cerebrospinal fluid Aβ1–42 levels (46). Variations in HBEGF are associated with AD risk (47) and intelligence (41).

3.4 Pathway analysis indicates an important role in regulation of mitochondrial functions by Vitamin D

According to the pathway enrichment analysis on DEGs after Vitamin D exposure, Vitamin D mainly enhances mitochondrial functions annotated by Gene Ontology (GO) database

(48) or Broad MSigDB (49, 50), such as mitochondrial membrane (GO), mitochondrial inner membrane (GO), genes involved in the citric acid (TCA) cycle and respiratory electron transport (Broad MSigDB), cellular respiration (GO), mitochondrial matrix (GO), generation of precursor metabolites and energy (GO), mitochondrial membrane part (GO), genes involved in respiratory electron transport, ATP synthesis by chemiosmotic coupling and heat production by uncoupling proteins (Broad MSigDB), and energy derivation by oxidation of organic compounds (GO). Immune response-related pathways such as innate immune response (GO), regulation of defense response (GO), and inflammatory response (GO), are also on the top of the listed pathways (Table S5).

3.5 Association of Vitamin D usage with decline of cognitive function

The baseline characteristics of patients ever or not on Vitamin D during follow-up are shown on Table S6. The baseline MMSE is slightly higher for the subjects ever on Vitamin D (22.5 +/− 4.1 vs 10.8 +/− 5). More subjects in the group ever on Vitamin D had more than 12 years education than those in the group never on Vitamin D (62% vs 45%). The mixed-effect model estimates that the decline rates in MMSE in the Vitamin D group and the non-Vitamin D group are 1.84 (95% CI: 1.49–2.18) MMSE /year and 2.11 (95% CI: 1.89, 2.33) MMSE/year, respectively ($F_{1,628}$=1.74, p=0.19).

4. Discussion

4.1 Vitamin D and psychosis

A link has been suggested between Vitamin D deficiency and the presence of schizophrenia-related symptoms by many studies. Adults and adolescents with higher dietary intakes of Vitamin D had a lower prevalence of psychotic-like symptoms in clinical observations. Patients with psychotic disorders were found to have lower Vitamin D levels than healthy controls, and this was mainly due to an observed association among schizophrenia patients (51). A similar conclusion was reached by a systematic review (52). Based on these reported studies, Vitamin D level has been significantly linked with psychotic symptoms and disorders, although our study is the first to extend this association to psychosis in AD. However, whether hypovitaminosis D may contribute mechanistically to psychosis, or is merely a correlate or confound, remains unknown.

4.2 Vitamin D and Alzheimer’s disease

Our findings are also congruent with prior evidence that Vitamin D deficiency is associated with cognitive impairment. Patients with AD have a high prevalence of Vitamin D deficiency, which is also associated with low mood and impaired cognitive performance in older people (53). A recent paper showed that the onset of hypovitaminosis D was accompanied by cognitive decline. Memantine was protective against hypovitaminosis D-related cognitive decline. This prompted a clinical trial of memantine together with Vitamin D for AD patients (NCT01409694), but no result has been released yet.

4.3 Role of Vitamin D receptor in AD and psychosis-related diseases

Vitamin D is recognized as playing several roles in the nervous system. The suggested protective effects of Vitamin D in AD were summarized (54) as the regulation of

neurotrophic factor production, neurotransmitter levels, oxidative stress mechanisms, calcium (Ca^{2+}) homeostasis and immune system functions, and induction of amyloid beta (Aβ) clearance (55–66). The molecular mechanism of Vitamin D on promoting Aβ clearance was reported to be through the recovery of Aβ phagocytosis by macrophages (65). In contrast, Vitamin D is not reported to affect accumulation of the other hallmark pathologic protein aggregate in AD, microtubule-associated protein tau (67).

Our pharmacogenomics analysis indicates that Vitamin D most likely regulates AD- and psychosis-related genes through the Vitamin D receptor (VDR), the bio-target of Vitamin D. In a small candidate gene study, polymorphism of the VDR gene was reported to be associated with AD (68), though this association has not been confirmed in GWAS analyses. In a functional study, both overexpression of VDR and Vitamin D treatment suppressed amyloid precursor protein (APP) transcription *in vitro* (69). Similarly, Vitamin D treatment in two AD mouse models reduced levels of soluble and insoluble Aβ and improved conditioned fear memory (70). Recently, our genetic association study of AD+P vs. AD-P patients found that polygenic risk for schizophrenia protects against the risk of psychosis in AD (71). Among the loci comprising this polygenic risk, we found that VDR can regulate the expression of TCF4 (indirect) (72) and CACNA1C (Calcium Voltage-Gated Channel Subunit Alpha1 C, down-regulate) (73). However, although these two genes are regulated by VDR, they were not among our most perturbed gene list. This may imply that their regulation is tissue-dependent as most of the biosets we used for the analysis were derived from non-neural cell types.

It would not be surprising if Vitamin D may modulate the AD progression to psychosis by regulating calcium (Ca^{2+}) homeostasis. The most important role of Vitamin D in the periphery is to maintain skeletal calcium balance by promoting calcium absorption in the intestines, promoting bone resorption by increasing osteoclast number, maintaining calcium and phosphate levels for bone formation, and allowing proper functioning of parathyroid hormone to maintain serum calcium levels. Other possible effects of Vitamin D treatment may include fueling mitochondria through increasing the expression of related proteins (74) or modulating the gene expression of AD or psychosis-related genes as indicated in Table 3.

We would like to point out some limitations of our study: the dosage information for Vitamin D was not available, as such, we just roughly classified the subjects as ever or never taking the medication. We did a sensitivity analysis using the proportion of visits on Vitamin D and duration of time on Vitamin D, results consistent with our analyses of ever versus never using Vitamin D (Supplemental Methods and Results). Also, secular trends exist in Vitamin D usage. That is, the use of Vitamin D was rare before year 2008 in our dataset, but its usage became frequent in later years (Table S7). Data collected from 2008 to present revealed a more significant protective effect of Vitamin D (Supplemental Methods and Results). Finally, we note that the studies of perturbation of gene expression by Vitamin D are conducted in model systems that either cannot (e.g. cell culture), or have not (animal models), evaluated the age-dependent effects of Vitamin D on the transcriptome and have not specifically evaluated the effects in brain. Thus, it is possible that other gene perturbations relevant to any possible effects of Vitamin D on reduced risk of psychosis in AD went undetected by our gene signature analyses.

5. Conclusions

Our clinical outcome analyses supported the protective association of Vitamin D with delayed onset and reduced occurrence of psychotic symptoms in AD patients. We did not find an association of Vitamin D use with rate of cognitive decline, suggesting that any effects of Vitamin D on psychosis risk are independent of signaling pathways associated with cognitive decline. The AD- and psychosis-related genes that are enriched in the dataset of genes most perturbed after Vitamin D exposure imply that Vitamin D might modulate AD progression via these genes. These mechanisms of action of Vitamin D could therefore provide leads to novel approaches for the reduction of psychosis in AD. Finally, some patients did take Vitamin D without beneficial effects on either cognitive functions or psychosis symptoms. This may indicate that only patients bearing risk alleles for genes influenced by Vitamin D can benefit from the Vitamin D treatment. If this latter hypothesis can be validated by well-designed clinical studies, it would provide valuable guidance for personalized AD treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Vitamin D was used more often in patients of Alzheimer's disease without psychosis symptoms than in patients of Alzheimer's disease with psychosis symptoms.
- Vitamin D use was significantly associated with delayed time to psychosis in Alzheimer's disease patients.
- The molecular mechanism of the beneficial effect might be attributed to the facts that Vitamin D can regulate Alzheimer's disease and/or psychosis-related genes.

Table 1.

Characteristics of subjects

Variable	AD-P, N=367	AD+P, N=256	df	p value*
Follow-up, years	2.5 (3.6)	3.3 (3.1)	595	0.003
Baseline MMSE	21.8 (4.5)	20.5 (5.3)	490	<0.001
Age at baseline	76.9 (6.9)	76.6 (6.4)	576	0.54
Sex				
female	214 (58 %)	164 (64 %)	1	0.15
male	153 (42 %)	92 (36 %)		
Race				
Asian	2(1%)	0(0%)	2	0.48
African-American	23 (6 %)	20 (8 %)		
Caucasian	342 (93 %)	236 (92 %)		
Number of drugs taken	9.7 (4.5)	8.6 (4)	587	0.002
Education, years				
<12	162 (44 %)	152 (59 %)	1	<0.001
>=12	205 (56 %)	104 (41 %)		

AD-P: Alzheimer Disease without psychosis; AD+P: Alzheimer disease with psychosis; MMSE:

Mini-mental State Examination.

Results for AD-P and AD+P are mean (SD) for continuous variables and total (%) for categorical variables.

*T-test for continuous variables (Follow-up, years; Baseline MMSE, Age at baseline), Chi-square test for sex and education, and Fisher exact test for race.

Table 2.

Use of Vitamin D in Alzheimer patients without and with psychosis

Vitamin D (Ergocalciferol)	AD-P, N (%)	AD+P, N (%)	Chi-square	df	FDR Adjusted p value*
No	237 (64.58%)	215 (83.98%)	28.5	1	<0.001
Yes	130 (35.42%)	41 (16.02%)			

AD-P: Alzheimer Disease without psychosis; AD+P: Alzheimer disease with psychosis *Chi-square test adjusted by Benjamini & Hochberg method

Table 3.

Cox regression analysis on time-to-onset of psychosis in Alzheimer's disease

Drug	HR (95% CI)	p value*
multivitamin	0.6 (0.47,0.78)	0.0001
memantine	0.66 (0.51,0.86)	0.002
Vitamin D(ergocalciferol)	0.68 (0.48,0.96)	0.03
omeprazole	0.77 (0.49,1.19)	0.24
warfarin	0.53 (0.3,0.91)	0.02
ferrous sulfate	0.24 (0.08,0.77)	0.02

*Multivariable Cox regression controlled for baseline MMSE, baseline age, sex, race, and education. p values were obtained by Wald chi-square test and df is 1 for each of the variables.

Table 4.

The fifteen most perturbed genes among 47 Vitamin D-induced biosets

Gene ID	Gene Name	Specificity	Evidence of association with AD- or schizophrenia - related phenotypes			
			Phenotype	SNP	Reported p value*	Ref.
CYP24A1	cytochrome P450, family 24, subfamily A, polypeptide 1	33 (32 up/1 down)/47				
EFTUD1	elongation factor Tu GTP binding domain containing 1	28(27 up/1 down)/47	cognitive ability	rs867371	1×10^{-10}	(40)
				rs2134046	2×10^{-8}	(40)
			Intelligence	rs28420834	1×10^{-10}	(41)
				rs1972460	2×10^{-10}	(41)
				rs2665103	4×10^{-10}	(41)
				rs12439619	1×10^{-8}	(41)
			educational attainment	rs28420834	3×10^{-10}	(42)
			left superior temporal gyrus thickness in schizophrenia patients	rs1466921	9×10^{-7}	(43)
CD14	CD14 molecule	27(26 up/1 down)/47				
CLMN	calmin (calponin-like, transmembrane)	27(26 up/1 down)/47	Cognitive decline in AD patients	rs115102486	2×10^{-8}	(44)
			response to perphenazine treatment	rs1187614	2×10^{-7}	(45)
MAPK13	mitogen-activated protein kinase 13	24(23 up/1 down)/47				
SERPINB1	serpin peptidase inhibitor, clade B (ovalbumin), member 1	24(23 up/ 1 down)/47	cerebrospinal fluid Aβ1–42 levels	rs316341	2×10^{-8}	(46)
CEBPB	CCAAT/enhancer binding protein (C/EBP), beta	23(22 up /1 down)/47				
THBD	Thrombomodulin	22 (21 up /1 down)/47				
G0S2	G0/G1switch 2	22(21 up /1 down)/47				
GEM	GTP binding protein overexpressed in skeletal muscle	22(21 up / 1 down)/47				
CD97	CD97 molecule	22(22 up)/47				
ACVRL1	activin A receptor type II-like 1	21(17 up/ 4 down)/47				
GRK5	G protein-coupled receptor kinase 5	21(19 up /2 down)/47				
HBEGF	heparin-binding EGF-like growth factor	20(18 up /2 down)/47	AD risk	rs11168036	7×10^{-9}	(47)
			Intelligence	rs2282802	5×10^{-9}	(41)
				rs2074613	1×10^{-8}	(41)
FOSL2	FOS-like antigen 2	20(18 up/2 down)/47				

*Reported p values were from literature (listed in Ref. column) reported genome-wide significance analysis (GWAS) studies.