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Report

Epidemiologic evidence supporting the role of maternal vitamin D deficiency as a risk factor for the development of infantile autism

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This study examines whether maternal vitamin D deficiency is a risk factor for infantile autism disease (IAD). We used epidemiologic data seasonal variation of birth rates and prevalence of IAD for cohorts born before 1985. For seven studies reporting spring-to-summer excess birth rates for IAD, the season progressed from broad near 30° N latitude, spring/summer in midlatitudes, to winter at the highest latitude. Also, using data from 10 studies, we found a strong effective latitudinal (related to wintertime solar ultraviolet B radiation) increase in IAD prevalence. These findings are consistent with maternal vitamin D deficiency's being a risk factor for IAD, possibly by affecting fetal brain development as well as possibly by affecting maternal immune system status during pregnancy. Further investigation of this hypothesis is warranted.

Introduction

The etiology of autism is still somewhat of an enigma. Autism is considered an autoimmune disease.[1] It also appears to have important risk factors in utero, as evidenced by a highly significant increased frequency of congenital malformations;[2] and those with autism have several characteristics associated with schizophrenia,[3] which is also linked to in utero risk factors.[4] Perinatal viral infection of mother or infant is a risk factor for both infantile autism and schizophrenia.[5] Also, several studies have reported seasonality in excess births of those with autism, with March being a peak month in Sweden,[6] Denmark[7] and Boston,[8] but without a good explanation for this seasonality.

Schizophrenia is another disease that exhibits excess of births in winter and a deficit in summer.[9] This seasonality has sometimes been shown to be linked to influenza epidemics.[10,11] Infectious disease during pregnancy has been found to adversely affect rodent brain development in a manner that can lead to schizophrenia as well as autism.[12-18] The hypothesis that the seasonality was related to low levels of maternal serum 25-hydroxyvitamin D (calcidiol) was also advanced.[19] Support for the maternal vitamin D deficiency hypothesis has been reported based on rat studies.[20-22]

It was recently proposed that the annual solar ultraviolet-B (UVB) and vitamin D cycles explained some of the seasonality of epidemic influenza, which peaks in winter.[23] This hypothesis received experimental support in a randomized, prospective, placebo-controlled vitamin D study involving 204 postmenopausal black women living in the state of New York. Those taking 2,000 IU of vitamin D3 per day got 10% as many colds or influenza as those taking the placebo.[24] More support came from a study of meteorological variables associated with incidence of respiratory syncytial virus that found an effect for solar UVB in addition to temperature and relative humidity, with greatest effect at lower latitude.[25] Thus, serum calcidiol levels can affect risk of maternal viral disease during pregnancy.

This report examines the evidence supporting the hypothesis that maternal vitamin D deficiency is an important risk factor for the development of infantile autism disease (IAD), through both direct effect and indirect effects in reducing the risk of infectious diseases. The analysis is limited to the period prior to the mid-1980s. There has been a rapid rise in birth rates of autism in countries such as the UK and the US since the mid-1980s.[26] While there is concern that increased rate of vaccinations, especially those containing Thimerosal, has led to the increases,[27] there is no general agreement that vaccinations are a cause of the increases.[28,29] Factors accounting for the increase include a broadening of diagnostic concepts and criteria, increased awareness and, therefore, better identification of children with pervasive developmental disorders in communities and epidemiologic surveys, and improved access to services.[30]

Results

Prevalence. Table 1 gives the regression results for IAD and their difference versus latitude. Figure 1 also shows the regression results for IAD. Effective latitude was highly correlated with prevalence; i.e., prevalence increased at the higher latitudes, which are associated with lower vitamin D produced by solar UVB in summer. Actual latitude was also correlated with prevalence data, but at lower levels of significance.

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Table 1 **Infantile autism disease (IAD) prevalence data for cohorts born before 1985**

Country, city	No. with autism; year of data collection	Diagnostic criteria	Prevalence per 10,000 (95% CI); age range	Reference
Israel	>200; 1960–82		1.4	31
USA, Minnesota	1990–6		52	32
North Dakota, USA	21; 1966–82	DSM-III, infantile	1.16 (1.4 age); 2–18 yrs	33
Wisconsin, USA	69; <1970		3.1 (3.6 age); 3–12 yrs	34
France (Rhone)	61; 1977–82	DSM-III, infantile	5.1 (3.9–6.3); 5–9 yrs	35
France	154; 1972, 76	ICD-9 (1978); infantile	4.9 (3.7–6.1); 9–13 yrs	36
UK	32; <1966	Kanner	4.1; 8–10 yrs	37
UK	17; <1976		4.9; 5–14 yrs	38
Ireland	28; 1968–70		4.3; 8–10 yrs	39
Denmark	20; <1970	Kanner	4.3 (5.2 age); 2–14 yrs	40
Sweden	20 (urban), 15 (rural); 1975–84	DSM-III; infantile	4.5 (4.2 rural, 4.7 urban) (5.6, 6.3 age); 0–9 years	41

However, people born between 1988 and 1995 showed little variation with latitude for IAD and an insignificant inverse correlation with latitude for PDD.

Season of birth. Figure 2 graphs the months of excess birth rate versus latitude, with December counted as month zero; when two adjacent quarters were listed as having excess birth rates, we omitted the two extreme months of these quarters. At the lower latitudes, there is a large spread, decreasing to 3–4 months for the other latitudes; also, there is a trend toward the beginning of the year with increasing latitude. New York does not fall into this pattern.

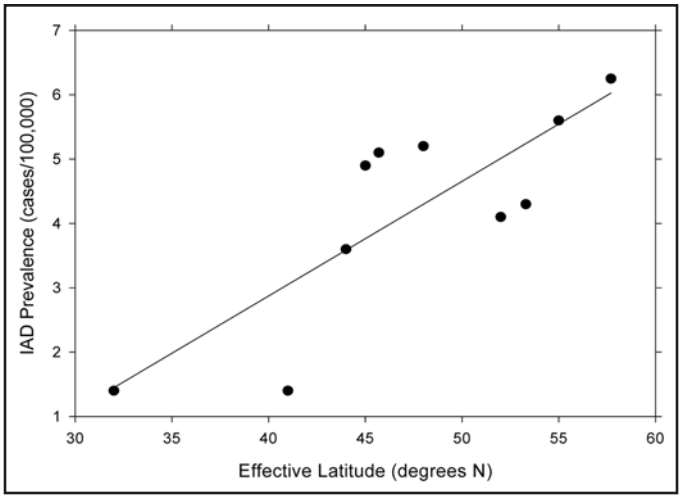

Figure 1. Prevalence of infantile autism disease for those born prior to 1985 vs. effective latitude.

Discussion

Prevalence and vitamin D deficiency. The data for seasonal variation of prevalence of those born prior to 1985 are consistent with an increased risk during pregnancy in winter. From the timing, risk is most likely affecting the mother during the third trimester of pregnancy since serum calcidiol values are lowest in late winter/early spring, and risk of influenza and other viral diseases is highest then. The brain develops mostly in the later stages of pregnancy, so a vitamin D deficiency would exert more effect during this period.[15] The prevalence of IAD quadruples in going from Israel to Sweden. The earlier period to the north is consistent with colder temperatures and lower solar UVB doses arriving earlier there than to the south. The fact that a similar effect was not found for the non-IAD portion of PDD, which develops after 30 months of age, is further evidence pointing to IAD's association with a maternal vitamin D deficiency.

The IAD prevalence data for France are somewhat above the regression line in Figure 1, perhaps partly because food there is not vitamin D fortified. On this basis, the French appear the largest winter/spring drop in serum calcidiol level of any country studied.[42] People living near the Arctic Circle are more likely to consume fish, an important source of vitamin D, and to take vitamin D supplements.

Infection and vitamin D deficiency. Multiple sclerosis (MS) is another disease for which risk increases rapidly with latitude.[43-45] The geographic variation in the US is more highly correlated with latitude, an index for wintertime UVB and vitamin D, than with July UVB.[43,46] Risk of MS is linked to the Epstein-Barr virus,[47] and both solar UVB[48] and vitamin D[49] reduce the risk. It has also been proposed that higher calcidiol levels reduce the risk of MS by reducing the risk of Epstein-Barr infection.[50]

Correlation of risk indices. The seasonal excess of autistic births has an interesting variation with latitude. The general coherence to the data indicates that there are seasonal influences on the risk of autism. The large spread in months of excess births for Israel—March, August and October—may be related to the fact that the latitude is low enough that there is not a pronounced seasonal variation of serum calcidiol levels. That the season of excess autistic birth is generally from December to April is consistent with a maternal vitamin D deficiency during the last 3–5 months of pregnancy. Serum calcidiol levels tend to be lowest in the spring at mid-to-higher latitudes as the body depletes vitamin D stores built up in the fatty tissues and photoproduction from solar UVB has

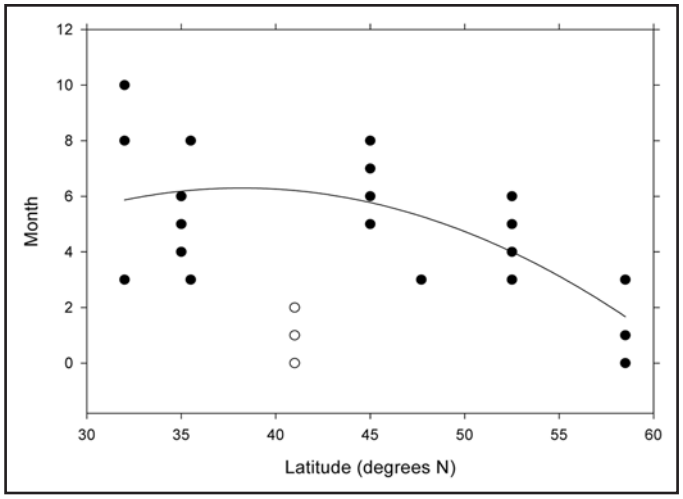

Figure 2. Months of the year with excess birth rates for autism vs. latitude of the country.

not yet resumed.[51] Curiously, however, serum calcidiol levels in Europe were found to increase with increasing latitude in winter,[52] which is probably due to higher cold water fish consumption, increased vitamin D fortification of food and use of supplements.

Positive role of vitamin D. Role of vitamin D in reducing the risk of IAD. Vitamin D could reduce the risk of IAD by (1) *aiding proper development of the brain* and/or (2) *strengthening the immune system*. The best evidence for a role of maternal calcidiol on brain development comes from the study of rat brain development for maternal vitamin D deficiency. Several adverse effects were found, such as reductions in brain content of nerve growth factor and glial cell line-derived neurotrophic factor, as well as structural differences of the cortex and lateral ventricles.[20] Other effects on rat brain development were reported more recently.[22,53]

Role of vitamin D in resistance to infection. Recent reports indicate that vitamin D *reduces the risk of respiratory diseases caused by viral infections*,[23-25] which are most common in winter. Other reports indicate that maternal influenza during pregnancy can adversely affect brain development.[11,12] Edwards indicates that hyperthermia during infectious diseases such as influenza can adversely affect fetal brain development and lead to birth defects such as later-life schizophrenia.[54] Taken together, these studies provide good evidence that vitamin D can affect development of the brain in utero by improving the immune system to reduce the risk of infectious diseases.

Possible role of infectious agents. *Maternal viral infection* is known to increase the risk for schizophrenia and autism in the offspring.[5] Animal models support this finding. Mice exposed to human influenza virus on Day 9 of pregnancy produced offspring with adverse effects on the developing brain including altered pyramidal and nonpyramidal cell density values; atrophy of pyramidal cells despite normal cell proliferation rate and final enlargement of brain.[14] In a subsequent study, prenatal viral infection showed significant upregulation of 21 genes and downregulation of 18 genes in the affected neonatal brain homogenates spanning gene families affecting cell structure and function.[14] Another study found that infection of mice with human influenza virus yielded offspring that displayed highly abnormal behavioral responses as adults. The effect was attributed to an effect of maternal immune response on the fetus.[12]

Application of these findings. The finding that vitamin D can reduce the risk of infectious diseases and that seasonal and latitudinal variations in solar UVB doses seems to *explain some of the epidemiology* of IAD prior to 1985 suggests that increased calcidiol levels during pregnancy, breast feeding, and infancy could reduce the risk of autism. While the role of vaccinations in the etiology of autism is not clear, higher levels of calcidiol could reduce the risk of adverse reactions to vaccinations, based on reports that calcidiol reduces the risk of respiratory viral infections and that calcitriol enhances the effectiveness of vaccinations.[55-58]

Materials and Methods

We searched the literature for relevant reports relating to prevalence of and seasonality of birth of childhood autism. For prevalence, several reviews were.[59-62] Several ideas were readily apparent in reviewing the published prevalence data:

(1) both IAD (defined as developing autism prior to 30 months of age) and pervasive developmental disorders (PDD) were studied;

(2) the criteria for determination changed several times since the original criteria developed by Kanner[63] for "nuclear autism";

(3) the prevalence rates varied geographically;

(4) the autism rates determined in Japan and other Asian countries were considerably higher than those determined in primarily white countries; and

(5) the prevalence rates increased when the DSM-III criteria were replaced by the DSM-III-R criteria.[64] This finding is related to a broadening of the diagnostic boundaries.[65] On the basis of these observations, the prevalence data used to investigate a possible latitudinal variation were restricted to those gathered using DSM-III and earlier criteria. Some of the subsequent data were used separately.

Tabular parameters and adjustments. Tables 2 and 3 give the *prevalence data* used in this study. We omitted data for Asian countries since the prevalence values are much higher than those in western developed countries. For Utah, an educated guess was to associate the prevalence stated as for "autism" with that for PDD since in Table 2 of that paper, many of the prevalence values from other reports are listed as associated with autism but are, in fact, associated with PDD. Also, the report states merely that DSM-III criteria were used. Also, some adjustments had to be made to account for different age ranges included in the various studies since even though IAD develops prior to 30 months of age, health officials often do not learn about student IAD status until the children attend school. The variation in observed prevalence rate versus age tabulated in Cialdella and Mamelle[35] was used to determine an effective prevalence for those values that included those younger than 5 years, 1.2 starting at age 3 years, and 1.33 starting at 0 years.

Several reports have looked for *seasonality* in autistic births. Table 4 summarizes the results of searching the National Library

Table 2 **Pervasive development disorder (PDD) prevalence data for cohorts born before 1985**

Country, city	Number with PDD; year of data collection	Diagnostic criteria	Prevalence per 10,000 (95% CI); age range	Reference
USA, Utah	241; 1975–79, 1980–4	DSM-III; PDD?	4.0; 8–12 yrs	66
North Dakota, USA	59; 1966–82	PDD	3.26 (4.0 age); 2–18 yrs	33
France (Rhone)	125; 1977–82	DSM-III	9.2; 5–9 yrs	35
UK	61; <1966	Kanner	7.8; 8–10 yrs	37
Denmark		Kanner	6.2 (7.4 age); 2–14 yrs	40
Sweden	25 (urban), 20 (rural); 1975–84	DSM-III; PDD	6.55 (5.6 rural, 7.5 urban) (7.45, 9.8 age); 0–9 years	41

Table 3 **Data relating to seasonality of autistic births**

Location	Latitude (°N)	Years	Period with highest rate of autistic births, in order	Enhancement ratio (to expected)	Reference
Israel	32	1964–86	August, March, October	2.2 (Aug.), 1.6 (Mar)	67
Japan	35		Second quarter		68
USA, North Carolina	35.5		March, August		69
USA, New York	41		Winter (January, February, March)		70
USA, Boston	43.3		March		8
Canada	45		Second quarter, third quarter		71
U.K.	52	1947–80	None found		72
Denmark	52.5	1945–80	March		7
Denmark, IQ <35	52.5	1923–92	Second quarter	1.3	73
Sweden	58.5	1962–84	March, January, December	2.2 (Mar.)	6

of Medicine's PubMed database. The winter and spring quarters had the highest rate of autistic births, with March being the month mentioned most often.

Hypothesis and test indices. The approaches used here to test the hypothesis that *maternal vitamin D deficiency is a risk factor for IAD and PDD include trying to find a link between vitamin D and IAD and PDD prevalence and interpreting the reported results regarding the seasonal variation in birth rates*. Thus, a suitable index for vitamin D at the population level must be used. The simplest index is *latitude*. Solar UVB radiation is the primary source of vitamin D for many people on Earth, especially in tropical and temperate climate zones. The well-documented seasonal variation of *serum calcidiol* shows the largest variation in countries, such as France, that do not fortify foods with vitamin D or encourage the use of vitamin D supplements.[74] However, in Europe in winter, serum calcidiol levels actually increase with latitude.[52]

There are *two simple indices for serum calcidiol assuming that solar UVB is the primary source*. The simplest one is *latitude* for latitude greater than about 30°. For example, those living near 30° can produce vitamin D from solar UVB during the entire year, whereas those living at 42° N cannot produce vitamin D from solar UVB for 4–5 months of the year.[35] However, this simple index cannot explain the geographic variation in US cancer mortality rates:[75,76] July UVB is much higher at the same latitude west of the Rocky Mountains than east of them.[77] Both lower column ozone and higher surface elevation west of the range explain the difference. The shift west of the Rockies is approximately 7° (770 km).[77] Also, from the finding that a state's degree of *urbanization* was an added risk factor for seven types of cancer for which UVB is a risk-reduction factor,[76] living in an urban versus a rural environment apparently reduces the total dose of UVB. Thus, latitude is used as the primary index for vitamin D, with slight adjustments for high summertime UVB levels and for living in a primarily rural region. Changes made to yield effective latitude for the prevalence data include the following:

- North Dakota, from 47.5° to 41° N
- Utah, from 41° to 35° N

Table 4 **Regression results for IAD and PDD prevalence for those born prior to 1985**

Disease	Latitudes	Adjusted r^2, F, p
IAD	Effective	0.63, 16, 0.004
	Actual	0.42, 7.4, 0.03
PDD	Effective	0.59, 9.5, 0.03
	Actual	0.23, 2.8, 0.15
PDD-IAD	Effective	-0.25, 0.01, 0.91
	Actual	-0.21, 0.12, 0.75

• Rural Bohuslän near Göteborg, from 57.7° N to 55° N

We ran multiple linear regressions with SigmaStat version 2.0, applying normality (Kolmogorov-Smirnov) and constant variance tests. For each linear regression, we give the values of the adjusted r^2, F (accounts for the number of degrees of freedom), and p.

Summary and Conclusion

The results presented here for season of birth and prevalence variation with effective latitude are consistent with maternal vitamin D's being a risk factor for development of IAD. However, in the late 1990s, the rates of IAD prevalence became several times higher than those prior to 1985, to the point where maternal vitamin D deficiency is no longer discernible in the epidemiologic data. Further work is required to determine whether vitamin D could be used to reduce the risk of autism, perhaps by reducing the risk of infectious disease or adverse reactions to vaccinations.

Note

This paper was largely written in 2004 and updated in 2008. Since that time, John J. Cannell has added further evidence for a role of vitamin D in reducing the risk of autism.[78,79] See also his ongoing discussion of the topic at his web site, http://vitamindcouncil.org/.

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