Risk Factors of Congenital Hypothyroidism in Israel

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ABSTRACT **Background:** Congenital hypothyroidism (CH) is the most common preventable cause of mental retardation and delayed growth in children. Several prenatal and environmental factors might be associated with the disease.

Objectives: To determine the prevalence and risk factors of permanent CH and transient congenital hypothyroidism (TCH) in Israel.

Methods: We conducted a retrospective analysis of the Israeli national newborn screening program database from 2011 to 2015. Chi-square and logistic regression were used to assess the association of the demographic and gestational factors with the CH and TCH.

Results: Of the 889,033 live births screened between 2011 and 2015, 860 were diagnosed with CH (9.76 per 10,000 live births) and 298 with TCH (3.35 per 10,000 live births). In multivariate analyses, CH was positively associated with female sex, gestational ages < 38 or > 39 weeks, birth weight < 3000 grams, and winter birth. A decreased risk of TCH was detected in Arabs and neonates from high socioeconomic areas. An increased risk was independently associated with gestational ages < 38 weeks, low birth weight, and winter birth.

Conclusions: Several demographic, gestational, and geographical factors are associated with the development of CH and TCH. Future studies are needed to further investigate the pathogenesis in Israel.

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KEY WORDS: congenital hypothyroidism, epidemiology, Israel, prevalence, risk factors

Congenital hypothyroidism is the most common preventable cause of mental and growth retardation in children and can only be prevented in cases of prompt diagnosis and early treatment [1]. Congenital hypothyroidism (CH) can be classified into permanent or transient congenital hypothyroidism (TCH) by persistence. While CH is a persistent deficiency of thyroid hormones that requires lifelong treatment, TCH is a temporary deficiency that reverts to normal concentrations with proper medical management, usually during the first few months of life and not after the age of 3 years [2]. Approximately 85% of CH cases are due to thyroid-dysgenesis, with the remainder attributed to dyshormonogenesis. The underlying etiology of CH due to thyroid dysgenesis is largely unknown. The majority of cases are sporadic, and only 2–5% of cases are found to be familial [3].

Many studies have suggested that TCH is less related to the development of the thyroid gland itself and more related to temporary, possibly environmental, factors that affect perinatal hormone concentrations. The most common is maternal iodine deficiency or overload [4]. Congenital hypothyroidism prevalence varies widely among countries, from 1:2000 to 1:4000 cases per live birth and has generally increased over the recent decades [1]. In Israel, the overall CH prevalence was 1:3,192 live births between 1978–1988 [5]. Using data from the Israeli national newborn screening program, we investigated risk factors and characterized the spatial trends of CH and TCH in Israel.

PATIENTS AND METHODS

STUDY DESIGN AND POPULATION

We conducted a historic cohort of neonates who participated in the Israeli newborn screening program between 2011 and 2015. The program covers almost 100% of the live births in the country, with all the samples analyzed by the national screening laboratory in Sheba Medical Center. Data about clinical diagnoses of CH and TCH, gestational age, birth weight, sex, date of birth, ethnicity, and official residential addresses were received from the Sheba Medical Center. The socioeconomic (SES) index was based on the Israel Central Bureau of Statistics based on geocoded residential addresses. The study was approved by the supreme ethics committee of the Israel Ministry of Health.

OUTCOME ASSESSMENT

Newborn screening tests for congenital hypothyroidism are routinely performed in Israel between 36–72 hours after birth, by measuring total thyroxine (TT4) concentrations in the blood. All heel-stick blood spot samples are analyzed by the screening lab at Sheba Medical Center. Levels of thyroid-stimulating hormone (TSH) are measured for neonates in the lowest daily TT4 decile. As hypothyroidism may develop in preterm neonates not immediately after birth, a second blood sample is obtained 7 days after birth, and a third one at one month of age or at discharge, whichever comes first. If TSH results of preterm birth are above 20 mU/L with TT4 below the bottom decile, a follow-up serum test of TSH and free thyroxine (FT4) is conducted. If TSH is above 10 mU/L or FT4 below 0.8 ng/dl, the preterm neonate

is referred to a specialized pediatric endocrinology unit at the hospital, and treatment with levothyroxine is initiated. The reference to the results of the second and third tests is like a test taken 36–72 hours after birth.

For term neonates, the procedure is different. Term neonates with TSH results above 40 mU/L are sent to a specialized pediatric endocrinology unit at the hospital where medical evaluation continues for further clinical evaluations. If TSH results are between 20–40 mU/L, the term neonate is referred to a second screening test in the community, followed by a subsequent measurement of TSH for term neonates with the lowest daily TT4 decile. When the subsequent TSH measurement results are above 40 mU/L, the term neonates continue their medical evaluation at a specialized pediatric endocrinology unit at the hospital. Term neonates with a subsequent TSH result between 20–40 mU/L are referred to a pediatrician in the community for a follow-up serum test measuring TSH and FT4 concentrations. If the TSH test result is above 10 mU/L or the FT4 test result is lower than 0.8 ng/dl, the term neonate is referred to a specialized pediatric endocrinology unit at the hospital. Additional clinical investigations such as physical examination, antithyroid peroxidase antibodies, and possibly radiology mapping of the thyroid gland, are sometimes used in the process of diagnoses of CH and TCH. Final diagnoses are reported to the national screening lab. For neonates initially diagnosed with CH, the diagnosis may change into TCH until the age of 3 years. Such changes are diagnosed at the specialized pediatric endocrinology units and are reported to the national laboratory.

STATISTICAL ANALYSES

We calculated the prevalence of CH and TCH as the proportion of neonates diagnosed with CH or TCH from all live births over the study period and used the Wilson score interval [6] to calculate 95% confidence intervals (95%CI). Prevalence proportions and 95%CI by subgroups were calculated similarly. We described univariate associations of clinical CH and TCH diagnoses with demographic and gestational factors in bar plots and analyzed these distributions by chi-square tests. We further applied logistic regression models to evaluate the independent association of each factor with CH and TCH. Last, we mapped the spatial distribution of congenital hypothyroidism prevalence in Israel using QGIS software version 3.10 [7]. Statistical. Statistical analysis was performed using R Statistical Software (version 3.4.2, R Foundation for Statistical Computing, Vienna, Austria) [8].

RESULTS

STUDY POPULATION AND PREVALENCE OF CH AND TCH

Between 2011 and 2015, the screening program in Israel screened 889,033 neonates. Their characteristics are described in Table 1. Approximately 70% of the neonates were Jews and 20% were Arabs, with about 8% born with low birth weight (< 2500 grams). Pediatric endocrinologists eventually diagnosed 860 of these neonates with CH, and 298 with TCH, resulting in prevalence proportions of 9.67 and 3.35 per 10,000 live births, respectively. When examining the spatial distribution of congenital hypothyroidism, we found that the prevalence was higher in the northern and southern areas and lower in center areas, with the highest prevalence of 17.9 per 10,000 live births in the Kinneret sub-district and the lowest of 6.4 per 10,000 live births in Jerusalem [Figure 1].

PREDICTORS OF CH AND TCH IN UNIVARIATE ANALYSES

We found a higher prevalence of CH among female neonates compared to males (10.9 and 8.5 per 10,000 live births, respectively), but an opposite picture for TCH (3.1 and 3.6 per 10,000 live births). The highest prevalence of CH and TCH was in winter births (11 and 4.2 per 10,000 live births, respectively), while the lowest was among those born in the summer. The prevalence of CH was higher among Arabs (10.7 per 10,000 live births) compared to Jews (9.6 per 10,000 live births), but TCH was less prevalent among Arab neonates (2.9 and 3.5 per 10,000 live births, respectively). In addition, we found that the lower the SES category, the higher the prevalence of both CH and TCH. However, the differences in CH and TCH prevalence by ethnicity or SES were not statistically significant.

CH was associated with gestational age in an inverse J-shaped curve, with the highest prevalence among neonates with gestational age < 34 weeks, but a slightly increased prevalence also in post-term neonates. The association of gestational age with TCH prevalence was weaker, and while early birth implied higher prevalence, post-term pregnancy was not associated with higher prevalence in comparison with term neonates. We found that CH was much higher with lower birth weights, with a similar picture for TCH. The prevalence of CH and TCH was higher among multiple gestation neonates (39.7 and 8.8 per 10,000 live births, respectively) compared to singletons (8.9 and 3.2 per 10,000 live births, respectively). The prevalence and univariate associations of the various predictors with CH and TCH are summarized in Table 1.

PREDICTORS OF CH AND TCH IN MULTIVARIATE ANALYSES

After applying the multiple logistic regression models, we found that the risk of CH was significantly higher for females than males (odds ratio [OR] 1.33, 95%CI 1.14–1.54) and for neonates born in the winter compared to those born in the summer (OR 1.31, 95%CI 1.06–1.61). The multivariable model of CH indicated that gestational age > 39 weeks or < 38 weeks implied an increased risk of the disease compared to 38–39 weeks of gestation. In addition, birth weight < 3000 grams was associated with an increased risk of CH, and this risk increased with decreasing birth weight. However, ethnicity, SES, and birth plurality were not significantly associated with CH in the multivariate models. The multivariate

Table 1. Demographic and gestational characteristics of the study population (N=889,033)

Variable		Congenital hypothyroidism				Transient congenital hypothyroidism			
		n	Prevalence per 10,000 live births	95% confidence interval	*P**	n	Prevalence per 10,000 live births	95% confidence interval	*P**
Sex	Female	471	10.9	(9.9–11.9)	0.0003	136	3.1	(2.7–3.7)	0.3
	Male	389	8.5	(7.7–9.4)		162	3.6	(3–4.1)	
Ethnicity	Arabs	196	10.7	(8.9–10.4)	0.2	54	2.9	(3.1–4)	0.2
	Jews	609	9.6	(9.3–12.3)		225	3.5	(2.2–3.8)	
Socioeconomic status	1–4	337	11.1	(9.9–12.3)	0.2	132	4.3	(3.7–5.1)	0.2
	5–6**	149	9.8	(8.3–11.5)	1	54	3.5	(2.7–4.6)	1
	7–10	278	9.1	(8.1–10.3)	0.5	86	2.8	(2.3–3.5)	0.2
Birth plurality	Singleton	779	8.9	(8.4–9.6)	< 0.0001	280	3.2	(2.9–3.6)	< 0.0001
	Multiple	81	39.7	(32–49.3)		18	8.8	(5.6–13.9)	
Gestational age, weeks	< 34	110	65.2	(54.1–78.5)	< 0.0001	–	–	–	–
	34–35	86	38.2	(31–47.2)	< 0.0001	–	–	–	–
	< 36	–	–	–	–	50	12.7	(9.6–16.7)	< 0.0001
	36–37	132	14.4	(12.2–17.1)	< 0.0001	67	7.3	(5.8–9.3)	< 0.0001
	38–39**	225	6.2	(5.5–7.1)	1	85	2.4	(1.9–2.9)	1
	40–41	256	7.2	(6.4–8.1)	0.1	89	2.5	(2–3.1)	0.8
	> 41	43	16.7	(12.4–22.5)	< 0.0001	6	2.3	(1.1–5.1)	1
Birth weight, grams	< 1500	61	76.4	(59.9–97.9)	< 0.0001	–	–	–	–
	1500–2000	87	65.5	(53.1-80.7)	< 0.0001	–	–	–	–
	< 2000	–	–	–	–	26	12.5	(8.5–18.3)	< 0.0001
	2000–2500	123	25.8	(21.6–30.7)	< 0.0001	63	13.2	(10.3–16.9)	< 0.0001
	2500–3000	172	8.9	(7.7–10.4)	0.001	65	3.4	(2.7–4.3)	0.001
	3000–3500**	218	6.2	(5.4–7)	1	76	2.2	(1.8–2.7)	1
	> 3500	163	6.7	(5.7–7.8)	0.6	58	2.3	(1.8–3.3)	0.7
Birth season	Winter	241	11	(9.7–12.4)	0.006	92	4.2	(3.4–5.1)	0.03
	Spring	209	10	(8.7–11.4)	0.08	69	3.3	(2.6–4.2)	0.5
	Summer**	190	8.4	(7.3–9.7)	1	65	2.8	(2.3–3.8)	1
	Autumn	220	9.4	(8.2–10.7)	0.2	70	3	(2.4–3.8)	0.9

*Significance level for a bivariate test of association using the chi-square test

**Reference

model of TCH demonstrated a significantly decreased risk of the disease for Arab neonates compared with Jews (OR 0.64, 95%CI 0.45–0.9) and for neonates in the highest SES category compared with those from the middle SES category (OR 0.66, 95%CI 0.46–0.93). We found a significantly increased risk of TCH among neonates with gestational age < 38 weeks (compared with those born at 38–39 weeks), neonates with a birth weight < 2500 grams (compared with a birth weight of 3000–3500 grams), and neonates born in the winter season compared to the summer season, but no significant associations with the neonate sex or with birth plurality. The complete results of these models are specified and summarized in Table 2 and Figure 2.

DISCUSSION

The overall prevalence of CH and TCH in Israel was 9.67 and 3.35 per 10,000 live births, respectively from 2011 to 2015. The results of our study indicated that female sex, gestational ages < 38 or > 39 weeks, birth weight < 3000 grams, and a winter-birth were associated with increased risk of CH independent of the other factors for which we accounted. We observed a decreased risk of TCH in Arabs and high SES, and increased risk associated with gestational ages < 38 weeks, low birth weight, and winter-birth, independently of the other factors. We showed that

Figure 1. Spatial distribution of congenital hypothyroidism in Israel by subdistricts based on residential addresses of 889,033 neonates born during 2011–2015

CHT = congenital hypothyroidism

the prevalence of CH has nearly tripled over the past decades (1:3192 in 1978–1988 [5] to 9.67:10,000 in 2011–2015). The increased prevalence can possibly be explained by different reasons. The major factor is due to the lowering of TSH screening thresholds for diagnosis, which has led to increased detection of milder cases. The other possible factor is the improved survival of preterm and low birth weight infants due to the improvement of the perinatal and neonatal intensive care services over time in Israel [9].

We demonstrated geographic variation in the prevalence of congenital hypothyroidism across different regions in Israel, consistent with a previous study from the 1980s [10]. Several studies from other countries also found that CH, but not TCH, is more common in females [11,12]. The preponderance of female cases of CH is mostly associated with dysgenesis of the thyroid gland [13,14]. Studies from other countries have demonstrated a varying prevalence of CH among ethnic groups, possibly related to genetic background [15,16]. In Israel, a previous study showed that CH incidence was lower among offspring of mothers and fathers of Israeli origin and higher among those of African mothers and Asian fathers [17].

Our study expanded the previously studied ethnic groups to include the Arab population. The finding of the association of socioeconomic status with TCH was not observed before and may be explained by accessibility to prenatal health care. The association between gestational age and CH or TCH is widely documented [13].

Our results extended these findings showing an inverse J-shaped association between CH and gestational age. Previous studies observed an association of CH with both extremes of the birth weight scale using multiple logistic regression, while TCH was associated with low-birth weight in univariate analyses [11,18]. We have shown that after adjustment of other factors, CH and TCH are associated with birth weights < 3000 and < 2500 grams, respectively. In addition, despite the common association of twinning with CH, this association is rarely seen in multivariable models [19,20]. Our results showed that the association of CH and TCH with birth plurality is not significant after accounting for gestational age and birth weight. The associations between seasonal variation, CH, and TCH remain inconsistent. In Japan, the monthly incidence of CH had statistically significant temperature-associated seasonal trends, where from January to December higher prevalence of CH was associated with lower temperatures [21]. In North England, no significant seasonal variation was observed in the incidence of CH [22]. In northwest Iran, a significant association was observed between the winter season and CH; however, no significant associations were detected in central Iran [19,23]. In Israel, during 1978–1988 the average monthly incidence showed a minimum in August; however, these seasonal variations were not statistically significant [5]. Our results showed significant associations between CH, TCH, and the birth sea-

Table 2. Logistic regression models of variables associated with congenital hypothyroidism and transient congenital hypothyroidism

	Congenital hypothyroidism						Transient congenital hypothyroidism					
	Univariate analysis			Multivariate analysis*			Univariate analysis			Multivariate analysis*		
	Odds ratio	95% confidence interval	*P* value	Adjusted odds ratio	95% confidence interval	*P* value	Odds ratio	95% confidence interval	*P* value	Adjusted odds ratio	95% confidence interval	*P* value
Sex (female vs. male)	1.39	1.2–1.62	<0.001	1.33	1.14–1.54	<0.001	0.95	0.74–1.22	0.7	0.91	0.71–1.18	0.5
Ethnicity (Arab vs. Jews)	1.17	0.99–1.39	0.07	1.11	0.91–1.34	0.3	0.83	0.61–1.14	0.2	0.64	0.45–0.9	0.01
Socioeconomic index												
1–4	1.08	0.88–1.32	0.5	1.05	0.86–1.3	0.6	1.02	0.74–1.41	0.9	1.14	0.82–1.58	0.4
5–6	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
7–10	0.93	0.76–1.15	0.5	0.95	0.76–1.17	0.6	0.73	0.51–1.02	0.07	0.66	0.46–0.93	0.02
Birth plurality (multiple vs. singleton)	4.48	3.48–5.76	< 0.001	1.3	0.98–1.72	0.06	2.86	1.73–4.75	< 0.001	0.87	0.51–1.49	0.6
Gestational age, week												
< 34	12.16	9.48–15.58	< 0.001	2.45	1.58–3.81	< 0.001	–	–	–	–	–	–
34–35	6.13	4.63–8.1	< 0.001	2.16	1.5–3.11	< 0.001	–	–	–	–	–	–
< 36	–	–	–	–	–	–	6.18	4.24–9	< 0.001	2.46	1.45–4.19	0.001
36–37	2.31	1.82–2.94	< 0.001	1.52	1.16–1.98	0.002	3.19	2.24–4.54	< 0.001	2.13	1.44–3.16	< 0.001
38–39	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
40–41	1.2	0.98–1.47	0.07	1.33	1.08–1.63	0.008	1.1	0.79–1.53	0.6	1.17	0.83–1.64	0.4
> 41	2.77	1.91–4.01	< 0.001	3.09	2.11–4.54	< 0.001	1.31	0.57–3.02	0.6	1.24	0.53–2.91	0.6
Birth weight, grams												
<1500	13.38	9.87–18.14	< 0.001	6.42	3.84–10.72	< 0.001	–	–	–	–	–	–
1500–2000	11.25	8.64–14.65	< 0.001	6.10	4.05–9.19	< 0.001	–	–	–	–	–	–
< 2000	–	–	–	–	–	–	6.54	4.12–10.38	< 0.001	3.39	1.77–6.49	< 0.001
2000–2500	3.87	3.04–4.95	< 0.001	2.91	2.14–3.96	< 0.001	6.34	4.43–9.07	< 0.001	4.1	2.6–6.47	< 0.001
2500–3000	1.41	1.14–1.76	0.002	1.37	1.09–1.72	0.006	1.53	1.07–2.2	0.02	1.37	0.94–2	0.1
3000–3500	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
> 3500	1.05	0.84–1.31	0.7	1.01	0.8–1.27	0.9	1.17	0.81–1.69	0.4	1.16	0.79–1.69	0.4
Birth season												
Winter	1.3	1.05–1.6	0.02	1.31	1.06–1.61	0.01	1.41	1–1.99	0.04	1.41	1–1.98	0.04
Spring	1.13	0.9–1.4	0.3	1.14	0.92–1.42	0.2	1.1	0.76–1.58	0.6	1.1	0.77–1.59	0.6
Summer	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Autumn	1.07	0.86–1.32	0.6	1.07	0.86–1.33	0.5	0.95	0.6–1.37	0.8	0.95	0.65–1.37	0.8

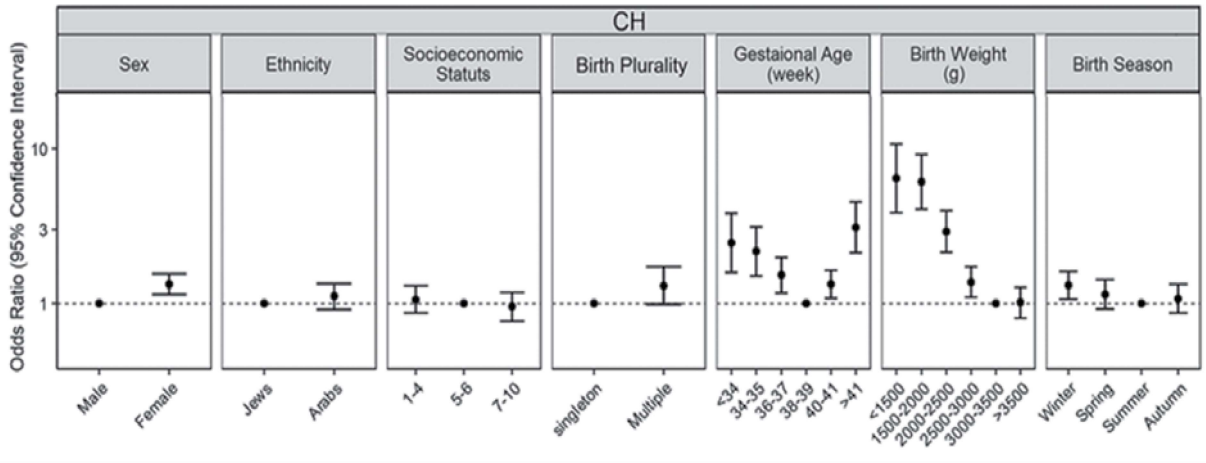
*Includes sex, ethnicity, socioeconomic, birth plurality, gestational age, birth weight, birth season

Ref = reference level

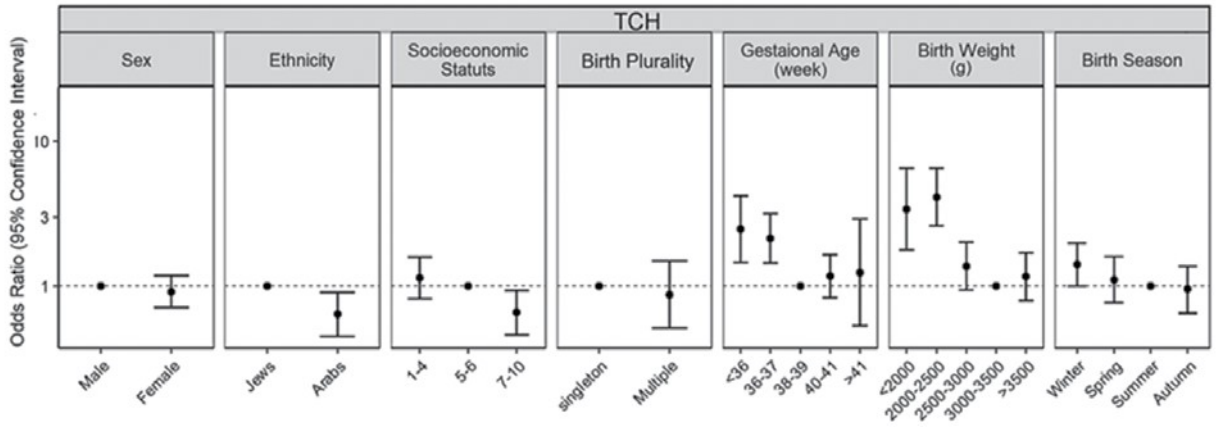
Figure 2. Coefficients of multiple logistic regression analyses of [A] permanent and [B] transient congenital hypothyroidism**.** The lines indicate the 95% confidence interval and the central points indicate the point estimates of the odds ratio

CH = congenital hypothyroidism, TCH = transient congenital hypothyroidism

[A] Permanent congenital hypothyroidism



[B] Transient congenital hypothyroidism



son. This association between TCH and the birth season was not studied before. Possible reasons for the seasonal variation in congenital hypothyroidism are viral infections, intrauterine infections of the fetus in early pregnancy, and seasonal differences in iodine concentrations [24,25]. The findings of this study provided more comprehensive and updated data on the epidemiology of CH in Israel and expanded previous findings to include TCH.

LIMITATIONS

The main limitation of the study is the lack of clinical data on the etiology of CH (dysgenesis vs. dyshormonogenesis), thyroid morphology, and biochemical severity of CH based on FT4 values at diagnosis. Our results warrant further investigations to better understand the pathogenesis of the disease.

CONCLUSIONS

The prevalence of CH and TCH have great variability across different regions in Israel and could be related to genetic, prenatal, and geographic factors. The results of this study can be used as a baseline to design future studies to further investigate the pathogenesis of TCH and CH, which may lead to an improved understanding of the pathogenesis of the disease and possible prevention strategies.

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Capsule

Medin co-aggregates with vascular amyloid-β in Alzheimer's disease

Aggregates of medin amyloid (a fragment of the protein MFG-E8, also known as lactadherin) are found in the vasculature of almost all humans over 50 years of age, making it the most common amyloid currently known. **Wagner** and colleagues recently reported that medin also aggregates in blood vessels of aging wild-type mice, causing cerebrovascular dysfunction. They demonstrated in amyloid-β precursor protein (APP) transgenic mice and in patients with Alzheimer's disease that medin co-localizes with vascular amyloid-β deposits, and that in mice, medin deficiency reduces vascular amyloid-β deposition by half. Moreover, in both the mouse and human brain, MFG-E8 is highly enriched in the vasculature and both MFG-E8 and medin levels increase with the severity of vascular amyloid-β burden. In addition, analyzing data from 566 individuals in the ROSMAP cohort, the authors found that patients with Alzheimer's disease have higher *MFGE8* expression levels, which are attributable to vascular cells and are associated with increased measures of cognitive decline, independent of plaque and tau pathology. Mechanistically, they demonstrate that medin interacts directly with amyloid-β to promote its aggregation, as medin forms heterologous fibrils with amyloid-β, affects amyloid-β fibril structure, and cross-seeds amyloid-β aggregation both in vitro and in vivo. Thus, medin could be a therapeutic target for prevention of vascular damage and cognitive decline resulting from amyloid-β deposition in the blood vessels of the brain.

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