Date of birth and the incidence of acute ischemic stroke in Hungary

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Introduction. The effect of the date of birth on the incidence of cardiovascular disease was confirmed in earlier studies. We aimed to determine whether the season of birth may be associated with a higher incidence of stroke in later life by analyzing thrombolysis numbers according over a ten-year period in Hungary.

Patients and methods. We analyzed daily thrombolysis numbers between 2007 and 2016 according to the patients' date of birth based on seasons. The correlation between cumulative thrombolysis numbers between 2007 and 2016 per month and birth numbers per month based on data of the 1949 census were also examined.

Results. Our results indicate that being born in the spring and summer in the northern hemisphere may be associated with a higher frequency of ischemic stroke necessitating thrombolytic treatment. This equates to a higher risk when conception and early pregnancy occur in the summer and autumn months.

Conclusions. This, however, cannot be defined as a causal relationship if we consider the number of live births in 1949, as both measures change similarly during the year, as indicated by the strong positive correlation between thrombolysis frequency according to date of birth between 2007 and 2016 and the number of births in the 1949 census by month.

Key words. Birth. Birthday. Conception. Incidence. Seasonality. Thrombolysis.

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Introduction

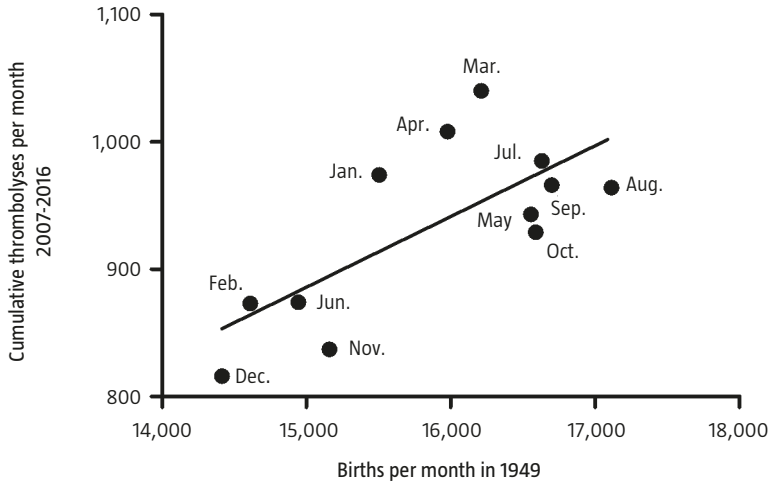
Linking the onset of stroke to various environmental influences and events enables the identification of etiological associations. The majority of these associations can be well explained by medical risk factors (such as hypertension, diabetes, hyperlipidemia, atrial fibrillation, or depression) and other causes (such as meteorological factors or air pollution). In contrast, other associations cannot be explained merely by biological impact, having in part individual and in part population-level psychological and sociological underlying causes. The role of complex sociocultural factors in the onset of cardiovascular events can be identified underlying the higher stroke risk of patients with low income [1], as well as in social occasions and holidays with significant emotional impact [2].

The literature already considers the connection with the date of birth to be confirmed in a number of diseases (e.g., multiple sclerosis, other autoimmune disorders, tumorous diseases, cardiovascular disorders, and anorexia nervosa). Essentially, biological and environmental causes are presumed to underlie this association, including whether pregnancy takes place in a season predisposing to infections or illnesses. The assessment of this question is hampered by the fact that the number of childbirths themselves is not steady during the year; therefore, it can be postulated that a larger number of births in a specific period will be associated with a higher incidence of stroke decades later, even without any causal relationship.

Thrombolytic therapy is useful to determine the precise onset of acute ischemic stroke due to its narrow therapeutic time window. The treatment is performed based on the same indication at all points in time, and the intervention is accurately documented. If the sufficiently high thrombolysis rate (i.e., the ratio of thrombolyses per total number of acute ischemic stroke cases) of a specific country is known, reliable data can be obtained about the frequency of acute ischemic stroke even if only a relatively limited number of patients are eligible for the therapy. The determination of the onset enables the analysis of the association of stroke with other events.

In this study, we aimed to determine whether the season of birth may be associated with a higher incidence of stroke in later life by analyzing throm-

Figure. Correlation analysis between thrombolysis frequency according to date of birth between 2007 and 2016 and the number of births in the 1949 census by month revealed a significant correlation (r = 0.726, p = 0.008).



bolysis numbers according to patients' date of birth over a ten-year period in Hungary.

Patients and methods

First, the cumulative number of daily thrombolyses performed in Hungary with the indication of acute ischemic stroke on any given day between 1 January 2007 and 31 December 2016 was analyzed, irrespective of the date of birth. Anonymized data were provided by the National Institute of Health Insurance Fund Management and its predecessor in law.

This was followed by the analysis of thrombolysis number according to the patients' date of birth based on seasons. The χ^2 test was used to determine statistical significance. p values less than 0.05 were considered significant.

Finally, the correlation between cumulative thrombolysis numbers between 2007 and 2016 per month and birth numbers per month based on data of the 1949 census was analyzed. Pearson's correlation was used for this analysis.

Results

A total of 11,209 thrombolyses conducted between 2007 and 2016 were analyzed. First, irrespective of the date of birth, the calendar days were arranged based on the number of treatments performed. The cumulative number of treatments performed was <28 on 113 days, between 28 and 33 on 147 days, and >33 on 106 days. Apart from the leap day February 29, the lowest cumulative number, 12 thrombolyses over the years analyzed were performed on December 17. The highest number of thrombolyses, 57 in total over the years analyzed, were performed on January 1. Interestingly, in addition to New Year's Day, the next two highest thrombolysis numbers, with 50 and 47 interventions performed, were related to Hungarian national holidays on March 15 and May 1, respectively.

We next analyzed the number of thrombolyses performed according to the date of birth of the patient season by season. An advantage of this approach is that it helps to mitigate the distortive effect of possible preterm births. We analyzed the number of calendar days of birth with <28 or >33 thrombolytic interventions performed in patients born in a given season (spring: March-May, summer: June-August, autumn: September-November, winter: December-February). The same analysis was performed for the most likely time point of conception (i.e., given season + 3 months) as well. The lowest frequency of days with a thrombolysis number of <28 was observed in the spring (19 days), which showed an increase in the subsequent seasons (in the summer: 23 days, in the autumn: 30 days, and in the winter: 41 days). The frequency of days with a treatment number of >33 showed quite the opposite tendency (in the spring: 36 days, in the summer: 26 days, in the autumn: 24 days, and in the winter: 20 days). The p value was less than 0.05 for all comparisons using the χ^2 test. Based on this, it can be presumed that being born in the spring and summer are associated with a higher frequency of ischemic stroke. This equates to a higher risk when conception and early pregnancy occur in the summer and autumn months.

When analyzing the association between thrombolysis frequency according to date of birth between 2007 and 2016 and the number of births in the 1949 census by month, a significant correlation could be observed (r = 0.726, p = 0.008) (Figure).

Discussion

Date of birth as a risk factor

According to Doblhammer and Vaupel, the date of birth influences the life expectancy of a person; however, this impact appears only over 50 years of

age and is independent of disease. Among people in Austria and Denmark (northern hemisphere), those who were born between October and December live longer that those between April and June. The association is quite the opposite in the southern hemisphere. Life expectancy based on the date of birth is independent of the seasonal change in mortality and socioeconomic differences. Furthermore, the difference in life expectancy based on the date of birth is continuously and significantly decreasing [3].

Bovet et al found a 13.8% increase in mortality around the birthday of an individual, associated with specific diseases (such as heart attack or stroke) predominantly among women, as well as with suicide and accidents predominantly among men [4]. In contrast, however, Angermeyer et al could not confirm any effect of the date of birth on mortality [5].

Boland et al and Poltavskiy et al made observations regarding cardiovascular diseases. The risk was the highest among those born in March in case of atrial fibrillation, congestive heart disease and valvular heart disease, whereas the highest risk for hypertension was present among those born in January [6, 7]. Ueda et al found cardiovascular mortality to be the highest among those born in March-April, whereas the lowest among those born in November [8]. A similar observation was made by Li et al in a study conducted in Colombia, a country near the equator, expanding to both the northern and southern hemisphere [9].

Nonaka et al examined the distribution of mortality due to cerebrovascular diseases at the population level [10]. They suggested that the intrauterine and infantile development as well as breastfeeding play important roles in the risk for cardiovascular diseases in adulthood. They also took the monthly distribution of the number of births into account among those born between 1900 and 1959. A higher than expected (+8-23%) mortality risk was observed among those born in the summer between 1920 and 1949 (especially in men). This was significant in terms of intracerebral hemorrhage, and a >10% increase in risk was observed for subarachnoid hemorrhage as well; however, no accumulation was observed with regards to ischemic stroke.

Number of births

The association between the date of birth and the risk for a disease decades later cannot be assessed without analyzing the birth (conception) characteristics of the given population. This is because the frequency of conception shows a remarkable seasonality. If the number of births was increased decades earlier, the incidence of a condition will be necessarily higher as well. According to Fiddes et al, the association between the risk for a disease and the date of birth is influenced by numerous factors [11]. For instance, the role of vitamin D levels and T cell function have been highlighted in multiple sclerosis [12]. Those born in May were exposed to lower vitamin D levels during pregnancy than those born in November. This could impact on intrauterine thymic development and T cell differentiation and function in later life. However, other factors, such as the birth rate characteristics of a given country, or the year and even the place of birth (e.g., the distance from the equator) are more difficult to link with similar physiological mechanisms. Therefore, presumed associations may be falsely positive.

The frequency of conception is influenced by social, environmental, and biological impacts. The situation is further complicated by the fact that the seasonality of births (conceptions) has changed in the past years. While the spring-summer accumulation of conceptions is characteristic for a large part of Europe, this accumulation mostly takes place in the winter in the USA [12]. The temperature and light duration (photoperiodicity) both play a role. In non-industrialized countries, the number of childbirths is 60% higher in the most active period of the year compared to that in the least active period. A remarkable effect of industrialization can be observed in case of Spain, where the number of births has changed since the eighties, with a shift in conception to the autumn-winter period [13]. Lerchl et al analyzed the seasonality of births in the period between 1951 and 1990 in Germany [14]. From the middle of the sixties until the middle of the seventies, the number of births reduced by half, and it has moderately increased since the middle of the eighties. A remarkable change occurred in terms of seasonality. Until 1970, the frequency of births was the highest in February-March, which later changed and was shifted to September.

Present findings

Our results indicate that being born in the spring and summer in the northern hemisphere may be associated with a higher frequency of ischemic stroke necessitating thrombolytic treatment. This equates to a higher risk when conception and early pregnancy occur in the summer and autumn months. This, however, cannot be defined as a causal relationship if we consider the number of live births in 1949, as both measures change similarly during the year, as indicated by the positive correla-

tion between thrombolysis frequency according to date of birth between 2007 and 2016 and the number of births in the 1949 census by month. This is due to the fact that the number of childbirths is not steady during the year; therefore, it can be postulated that a larger number of births in a specific period will be associated with a higher incidence of stroke decades later, even without any causal relationship.

Additional data out of the primary scope were also obtained in this study: irrespectively of the date of birth, New Year's Day and other national holidays represent a remarkable risk for stroke, even though the latter group comprises less personal events and their psychological impacts are seemingly not decisive. However, these findings are in line with our previous findings describing that social occasions and holidays with significant emotional impact, such as Christmas increase the risk of stroke in vulnerable groups of the population [2].

Although our present findings support the association between the date of birth and the incidence of acute ischemic stroke, indicating that people born in the spring in Hungary are most likely, whereas those born in the winter are least likely to require future thrombolysis for ischemic stroke, we could not deem this association to be causative, and the association can at least be partially explained by the fluctuation of the number of births in Hungary when the population most prone to stroke was born. Further studies are needed to establish whether any other additional biological and/or social factors contribute to the spread of stroke incidence throughout the year described in this paper.

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Fecha de nacimiento e incidencia del ictus isquémico agudo en Hungría

Introducción. El efecto de la fecha de nacimiento sobre la incidencia de enfermedad cardiovascular se ha confirmado en estudios anteriores. Nuestro objetivo fue determinar si la temporada de nacimiento puede estar asociada con una mayor incidencia de accidente cerebrovascular en etapas posteriores de la vida mediante el análisis de las cifras de trombólisis durante un período de 10 años en Hungría.

Pacientes y métodos. Analizamos las cifras diarias de trombólisis entre 2007 y 2016 según la fecha de nacimiento de los pacientes según las estaciones. También se examinó la correlación entre las cifras de trombólisis acumuladas entre 2007 y 2016 por mes, y las cifras de nacimientos por mes según los datos del censo de 1949.

Resultados. Nuestros resultados indican que nacer en primavera y verano en el hemisferio norte puede estar asociado con una mayor frecuencia de accidentes cerebrovasculares isquémicos que requieren tratamiento trombolítico. Esto equivale a un mayor riesgo cuando la concepción y el embarazo temprano ocurren en los meses de verano y otoño.

Conclusión. Esto, sin embargo, no puede definirse como una relación causal si consideramos el número de nacidos vivos en 1949, ya que ambas medidas cambian de manera similar durante el año, como lo indica la fuerte correlación positiva entre la frecuencia de trombólisis según la fecha de nacimiento entre 2007 y 2016, y el número de nacimientos en el censo de 1949 por mes.

Palabras clave. Concepción. Cumpleaños. Estacionalidad. Incidencia. Nacimiento. Trombólisis.