Age-Period-Cohort Analysis of Creutzfeldt-Jakob Disease in Israel (1985–2019)

Yacov Balash MD PhD[1,2], Esther Kahana MD PhD[3,4], Ronit Gilad MD[1,2], Anda Eilam MD[1,2], and Amos D. Korczyn MD PhD[5,6]

[1]Department of Neurology, Kaplan Medical Center, Rehovot, Israel
[2]Hadassah Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel
[3]Department of Neurology, Barzilai Medical Center, Ashkelon, Israel
[4]Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel
[5]Department of Neurology, Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel
[6]Department of Physiology and Pharmacology, Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Although the epidemiology of Creutzfeldt-Jakob disease (CJD) in Israel has been studied extensively, it is unknown whether its incidence is mainly a result of vertical transmission due to the high penetrance of the E200K mutation in patients with familial CJD (f-CJD) compared to sporadic CJD (s-CJD), or whether there are other yet undiscovered contributing factors.

Objectives: To conduct an age-period-cohort (APC) analysis of Creutzfeldt-Jakob disease in Israel.

Methods: In this APC analysis, we used a web-based statistical tool to identify whether patient age, period of birth, and cohort had any effect on incidence trends of s-CJD and f-CJD.

Results: APC analysis demonstrated no significant shifts in net drift, indicating the absence of any overall trend of changes over time. Cohort analysis revealed that individuals affected by either s-CJD or f-CJD who were mostly born in Israel in the second half of the 20th century exhibited the same risk as those born mainly in Libya at the beginning of 20th century. There were no changes in risk of s-CJD and f-CJD between 1985 and 2019.

Conclusions: The incidence rates of s-CJD and f-CJD in Israel have remained unchanged, indicating that the probability of a future increase in the incidence is negligible.

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KEY WORDS: age-period-cohort (APC) analysis, Creutzfeldt-Jakob disease (CJD), familial Creutzfeldt-Jakob disease (f-CJD), incidence, sporadic Creutzfeldt-Jakob disease (s-CJD)

Creutzfeldt-Jakob disease (CJD) is a rare neurodegenerative disorder with an inevitable fatal prognosis. In Israel, its mean annual age-adjusted incidence is 1.88 ± 0.09 (95% confidence interval [95%CI] 1.7–2.08) per million for familial CJD (f-CJD) and 0.93 ± 0.06 (95%CI 0.81–1.06) per million for sporadic CJD (s-CJD) [1]. A similar difference between the incidence of f-CJD and that of s-CJD was found in the eastern regions of Slovakia [2], where the same genetic mutation in the *PRNP* gene (substitution of the amino acid glutamate for lysine in codon 200 or E200K) is common. The genetic variation of the disease (f-CJD) in these two clusters in Slovakia and in Israel (among immigrants from Libya and Tunisia) [3,4] is much less common worldwide. The genetic defect is based on an E200K mutation in the prion gene (*PRNP*) and it is the same in both clusters, although these two mutations occurred independently [5].

In contrast to Slovakia, Libya, and Tunisia, the most common form of human prion disease worldwide is s-CJD, which accounts for 85–90% of cases. Acquired CJD due to exposure via medical procedures (iatrogenic) or contaminated meat (variant CJD) accounts for < 1% [6].

Clinically, those forms of CJD appear to be indistinguishable and typically present with rapidly progressive dementia, cerebellar ataxia, extrapyramidal signs, myoclonus, and seizures with intense deterioration leading to death with a median survival time of 4–8 months [7]. In our experience, f-CJD may start 5–6 years earlier than s-CJD [1], thus affecting younger individuals.

In Israel, dissemination of the E200K mutation primarily occurs in the Libyan and Tunisian communities in which there is a relatively high frequency of the disease characterized by autosomal dominant inheritance with high penetrance [8].

In our previous work, we found no epidemiological data indicating horizontal transmission of either f-CJD or s-CJD [1]. However, whether a cumulative effect of these diseases that could manifest in successive generations and cause vertical transmission remains unclear. To date, no cases of prion disease transmission from mother to child (in utero or through breastfeeding) have been recorded, and children born to mothers with s-CJD or variant CJD remain healthy for decades.

Unlike humans, vertical transmission has been definitively confirmed in some animal species. In sheep, infectious scrapie prions are found in the placenta and are transmitted to lambs. In deer and elk, vertical transmission of prions causes epidemics of chronic wasting disease, and the risk of prion transmission from cow to calf in bovine spongiform encephalopathy is estimated at approximately 10%, although the mechanism of transmission is not fully understood. Thus, showing the same possibility in humans may be a matter of time and more advanced diagnostic techniques.

Recent longitudinal studies (2007–2020) have noted a rise in reported incidence of CJD in high-income countries, with rates in some areas reaching 1.5 to 1.6 per million. This rate is often attributed to the age-period-cohort (APC) effect, due to better diagnostic tools (like RT-QuIC testing). Real-time quaking-induced conversion (RT-QuIC) is a highly sensitive and nearly 100% specific laboratory assay used to detect misfolded prion proteins in cerebrospinal fluid. An increasing elderly population leads to more frequent and accurate identification of the disease [9].

To understand this issue better, we used APC analysis to disentangle the influence of these factors on the development of f-CJD and s-CJD disease over recent decades. This approach allowed us to examine the dynamics of disease incidence depending on age, period, and cohort. In the context of prion diseases, this analysis helps determine whether there is a risk of transmission of infection from mother to child through common environmental factors within the family. It is unknown whether patients with f-CJD or s-CJD exhibit a cohort effect (increased incidence among people born in certain years), a period effect (increase in disease incidence over time), or anticipation (characterized by an earlier onset of the disease in subsequent generations), as is common in some genetic neurodegenerative diseases.

We investigated the impact of APC components on the trend of the incidence rates f-CJD among mainly Libyan and Tunisian immigrants compared to the trend of s-CJD among mainly European and Asian immigrants as well that offspring of both groups born in Israel between 1985 and 2019, when modern diagnostic criteria for CJD were implemented.

PATIENTS AND METHODS

ETHICS

This anonymized study was performed according to the principles of the Declaration of Helsinki. Approval was granted by the Barzilai Medical Center Institutional Review Board (protocol number: 0102-18-BRZ).

DATA SOURCE

This analysis included data from the Israeli National CJD Registry, which contains information on CJD cases from 1985 to 2019. Detailed information about the registry and the criteria for identification of CJD as either definite, probable, or possible have been recorded [1,10].

STATISTICAL ANALYSIS

We conducted an APC analysis using a web-based statistical tool to examine the factors potentially influencing the incidence of f-CJD and s-CJD rates in Israel between 1985 to 2019 (https://analysistools.nci.nih.gov/apc/). The APC analysis is a parametric statistical method providing information about the effects of APC on the trend in disease rates. The input data included incident CJD cases and Israeli population size. The CJD patients were divided into nine 5-year age groups (40–44 to 80–84) for s-CJD and ten 5-year age groups (35–39 to 80–84) for f-CJD. The patients with f-CJD were younger and were distributed among seven 5-year periods (1985–1989 to 2015–2019) The statistical tool we used required equal time intervals (in this case, 5 years) across both age groups and observation periods. The default APC for reference were the median values of each category. The components of the APC analysis in this study were the longitudinal age curve, period, and cohort rate ratios (RR), net drift, and local drifts. The longitudinal age curve reflected longitudinal age rates in the reference cohort adjusted for period variations. The period RR was the ratio of age rates in each period as related to the reference period. The cohort RR was the ratio of age rates in each cohort as related to the reference cohort. The net drift represented the overall log-linear trend by calendar period and birth cohort, indicating the overall annual percent change. Conversely, local drifts reflected the log-linear trend by calendar period and birth cohort for each age group, providing the annual percent change for each age group.

The two-tailed Wald chi-square test was used for the hypothesis proof (the null hypothesis suggested that all cohort RR=1). A P-value < 0.05 was considered statistically significant.

RESULTS

A total of 638 individuals (age range 35–84 years, 315 males) were diagnosed with CJD in Israel between 1985 and 2019. According to the CJD criteria [10], the diagnosis was definitive in 54 (8.5%), probable in 520 (81.5%),

and possibly in 64 (10%). Among the cohort, 414 (201 males) were diagnosed as having f-CJD and 224 (114 males) as having s-CJD.

The age at CJD onset remained stable throughout the entire periods of time. Specifically, the overall mean age of the patients with s-CJD was 66.0 ± 9.4 years and 60.5 ± 9.4 years for the f-CJD patients. The disease onset of patients with f-CJD was approximately 5.8 years earlier than that for s-CJD (both Mann-Whitney U and Wilcoxon signed-ranks, $P < 0.001$). The median survival time was 5.4 months (IQR is interquartile range between the third and the first quartiles IQR 3.4–11.9) for patients with f-CJD and 5.5 months (IQR: 3.1–13.6) for those with s-CJD.

Figure 1. Cohort rate ratios in patients with sporadic Creutzfeldt-Jakob disease and familial Creutzfeldt-Jakob disease
The shaded area represents the 95% confidence interval.

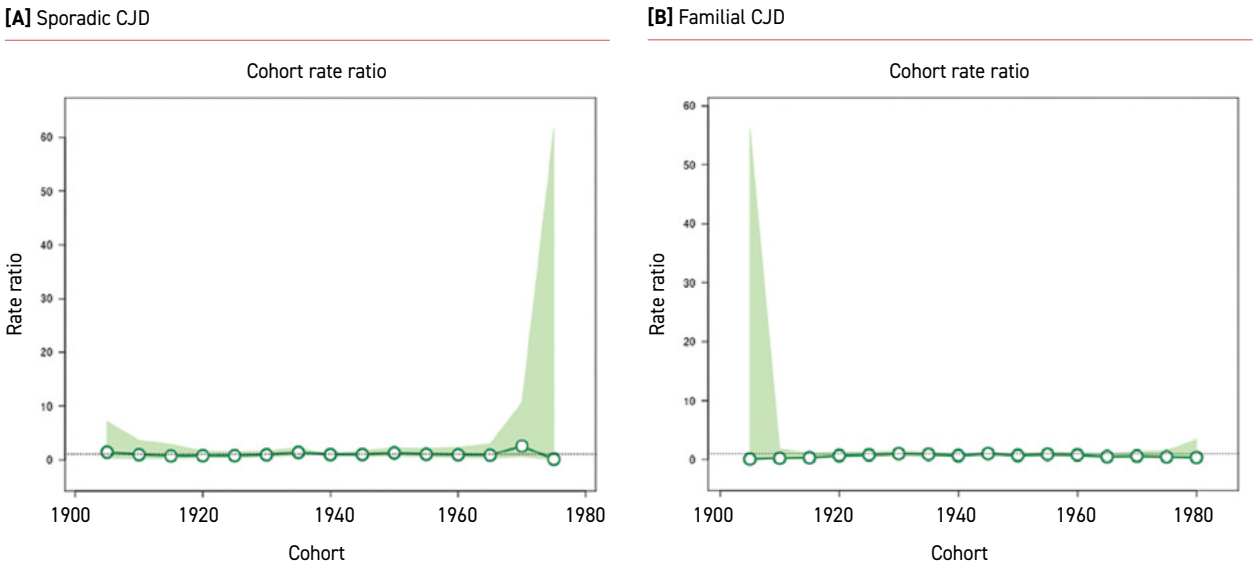
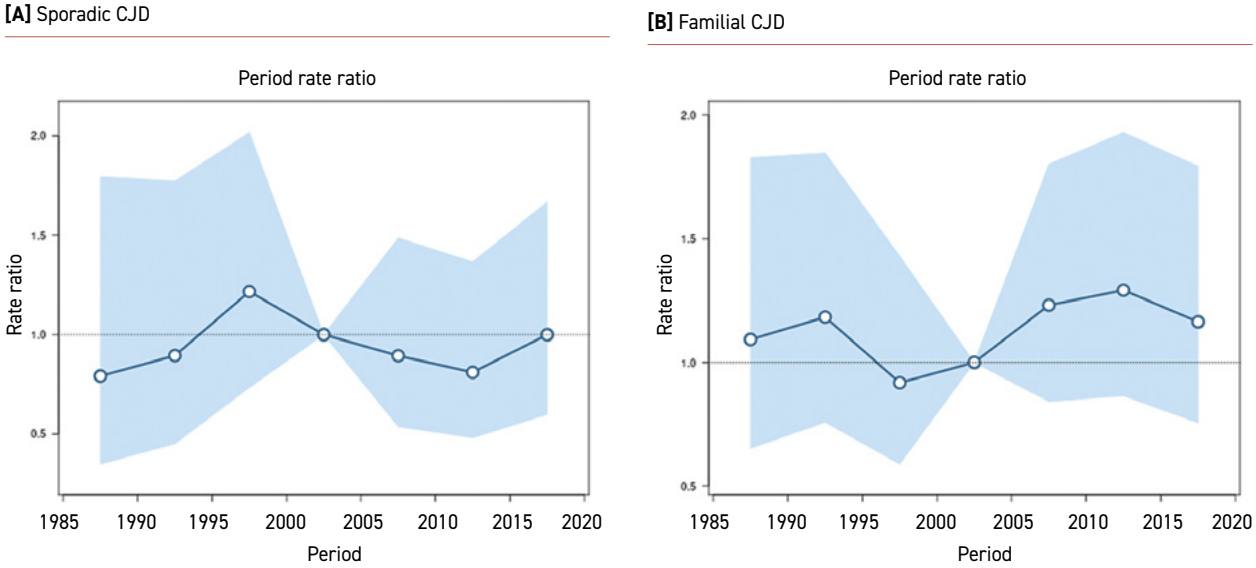


Figure 2. Period rate ratios in patients with sporadic Creutzfeldt-Jakob disease and familial Creutzfeldt-Jakob disease
The shaded area represents the 95% confidence interval.

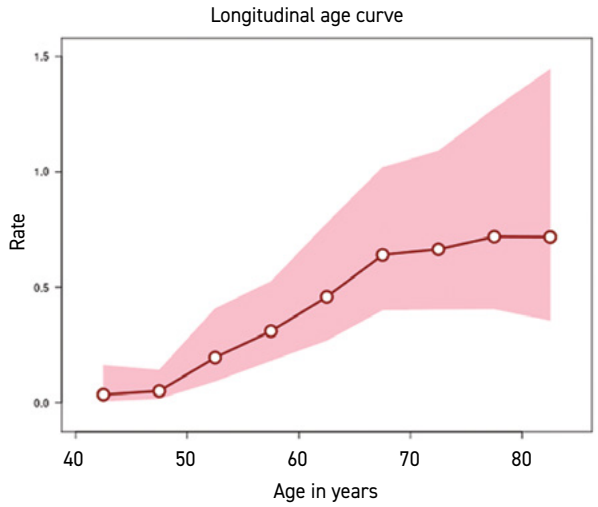


Immigrants from Libya and Tunisia (including second and third generations) prominently predominated among the cases of f-CJD, accounting for 377/414 cases (91.1%). Among the patients with s-CJD, 80 were Jewish Israelis and their forebears who had immigrated from Europe, 51 from Western and Central Asia, 41 from the former USSR, 29 from North Africa, and 7 from the Americas. In addition, 14 were Muslim Arabs, one was a Christian Arab, and one was a member of the Druze community.

Figure 3. Longitudinal age curves in patients with sporadic Creutzfeldt-Jakob disease and familial Creutzfeldt-Jakob disease

The shaded area represents the 95% confidence interval.

[A] Sporadic CJD



[B] Familial CJD

APC analysis demonstrated no significant shifts in net drift that would reflect an overall trend in the incidence of either f-CJD or s-CJD ($P = 0.591$ and $P = 0.904$, respectively). None of the cohort deviations and cohort RR were significant ($P = 0.769$ and $P = 0.801$ for s-CJD and $P = 0.664$ and $P = 0.438$ for f-CJD). These results indicate that the individuals with f-CJD as well as those with s-CJD who were born in the late 20th century exhibited the same risk of developing CJD as those who were born in the beginning of the 20th century [Figure 1]. Similarly, none of the period deviations and period RRs were significant ($P = 0.684$ and $P = 0.796$ for s-CJD and $P = 0.664$ and $P = 0.438$ for f-CJD) [Figure 2].

Age deviations were significant in both the f-CJD and s-CJD cohorts. The Wald chi-square test result was $P = 0.039$ for s-CJD and $P < 0.001$ for f-CJD. However, longitudinal age curves in patients with s-CJD and those with f-CJD differed. Specifically, while the risk of s-CJD increased with age and remained consistently high up to the oldest age of 84 years, it peaked in the 60-year age group and declined thereafter in patients with f-CJD [Figure 3].

DISCUSSION

Our results revealed that there were no changes in the risks of an increasing incidence of s-CJD and f-CJD from 1985 to 2019, in accordance with our previous observations obtained using joinpoint regression [1]. The birth cohort effect reflecting the impact of a possible external environment on the health status of a group born in a particular time, region, or exposure to the same events during the same timeframe was also insignificant. Last, no dynamics in epidemiological trends in incidence were detected in patients with either s-CJD or f-CJD throughout the entire 35-year period. Longitudinal age curves in patients with s-CJD and f-CJD were clearly different. In contrast to the f-CJD group, there was a different longitudinal age curve in patients with s-CJD for whom there was no decrease in incidence with age [Figure 3B]. The risk of s-CJD increased starting from the 45–49 year age group and remained consistently high up to the oldest age group of 84 years. While the etiology of f-CJD seems straightforward, several attempts have been made to find possible causes of s-CJD. These lines of investigation have proposed potential dietary, occupational, and medical etiologies.

Previously, APC analysis was used to study mortality rates in patients with s-CJD. In the study by Denouel et al. [11], mortality rates were higher in females at younger ages and lower at older ages.

The rates increased progressively with successive birth cohorts, which according to the authors, suggests that environmental exposures may play a role in the etiology of s-CJD. This analysis has not been used to study the incidence of s-CJD and f-CJD.

To definitively rule out the possibility of transmission of f-CJD in subsequent generations of Libyan and Tunisian Jews, the incidence of f-CJD in the third generation would need to be determined. Unfortunately, we were unable to obtain this information because the Central Bureau of Statistics classified the third generation as born in Israel, without specifying the origin of their ancestors, making it impossible to establish this connection.

Our APC analysis suggests that the likelihood of any increase in the incidence of f-CJD in the next generation of Libyan and Tunisian Jewish descendants is unlikely since the incidence rates of f-CJD have remained unchanged among all birth cohorts from 1905 to 1980 and over the entire 35-year observation period. Similarly, we did not observe any growth dynamics in the cohorts of s-CJD over that entire period. Therefore, vertical transmission of both forms of CJD did not result in a progressive increase of this disease in Israel.

The maximal incidence of f-CJD in our cohort was in the age range of 60-64 years [Figure 3A]. After this peak, the incidences of f-CJD progressively declined and there was no disease onset after 80 years of age, possibly because of a likely absence of any remaining E200K mutation carriers in this age group or due to the unlikelihood of some possibly epigenetic cause affecting PrP^{Sc} propagation. Since the mean age at f-CJD onset in our cohort was 60.5 ± 9.4 years, and given that the clinical symptoms of the disease appeared close to age 35 years at the earliest [1], it can be assumed that there are some individuals carrying the *PRNP* E200K mutation in the Libyan and Tunisian Jewish communities.

Chapman and colleagues [8] determined the penetrance of the *PRNP* E200K mutation in a relatively small group of f-CJD patients among Jews of Libyan Tunisian origin living in Israel (52 carriers with confirmed or probable CJD vs. 34 healthy carriers). In their work, the probability of developing f-CJD increased with age, approaching 100% by 80 years of age. However, their computations relied on incorporating older individuals suspected of having f-CJD who might have received unclear clinical diagnoses of f-CJD or encountered PCR uncertainties while amplifying the *PRNP* gene segment prior to its sequencing.

LIMITATIONS

A limitation of this study is the small number of pathologically confirmed cases of CJD in the Israeli National CJD Registry. This is due to religious attitudes and reluctance of the families to perform a brain biopsy on a relative who died from CJD. While these restraints reduced the number of definitive cases, they did not violate the criteria of Zerr and co-authors [10] and should not negatively affect the accuracy of this analysis.

CONCLUSIONS

This study is the first APC analysis of the incidence of CJD in Israel. We found no trend toward an increase in the incidence of either f-CJD or s-CJD in all selected birth cohorts since the beginning of the 20th century and over the past 35 years or at least two generations of Israelis. However, we found a significant age effect, in which the risk of s-CJD increased with age and remained consistently high up to the oldest ages, and which differed from the risks of f-CJD, which increased only up to age 60 years and then reduced.

We found no cohort effect indicating an increased incidence of f-CJD or s-CJD in individuals born in certain years, no period effect indicating an increase in the incidence of f-CJD over time, and no anticipation phenomenon indicating an earlier onset of CJD in subsequent generations. Earlier research, prior to the introduction of improved diagnostic methods for CJD, such as the RT-QuIC test or next-generation sequencing (NGS) may have been conducted. NGS has significantly improved genomics by sequencing millions of DNA fragments in parallel rather than one at a time, unlike the traditional Sanger method for detecting the E200K mutation.

In 2020, Cohen et al. [12] demonstrated the absence of anticipation in patients with f-CJD by comparing the age of f-CJD onset between first and second generations using an independent *t*-test.

The likelihood of an increase in the incidence of these diseases in the future (i.e., in the third generation of immigrants) seems unlikely. The longitudinal age curves in patients with s-CJD and f-CJD have different shapes reflecting differences in the biological properties of prions in terms of their replication. Further studies are needed to identify other risk factors for the development of these diseases in Israel.

Correspondence

Dr. Y. Balash
Dept. of Neurology, Kaplan Medical Center, Rehovot 7610041, Israel
Phone: (972-8) 944-0828
Fax: (972-8) 944-0829
Email: yacovbalash@gmail.com

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Capsule

Adaptive deep brain stimulation for dynamic gait control in Parkinson's disease: a randomized feasibility trial

Louie and colleagues evaluated a closed-loop adaptive deep brain stimulation (DBS) system designed to continuously modify stimulation in response to changes in neural biomarkers associated with gait and motor performance. Patients with Parkinson's disease and clinically significant gait impairment underwent both adaptive and conventional stimulation under randomized conditions. The adaptive stimulation system proved safe and technically feasible, with no unexpected device-related or treatment-related serious adverse events. Compared with conventional DBS, adaptive DBS demonstrated improvements in gait dynamics, including more stable walking, reduced gait variability, and fewer freezing episodes during challenging locomotor tasks. Patients also showed trends toward improved balance and mobility, suggesting that real-time adjustment of stimulation may better accommodate fluctuations in motor function during daily activities.

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Capsule

Activity-dependent adaptive deep brain stimulation improves gait in Parkinson's disease

Scafa and co-authors developed an activity-dependent adaptive deep brain stimulation (aDBS) system that continuously monitors neural signals associated with movement and automatically adjusts stimulation intensity during walking. The researchers investigated whether this physiologically driven approach could improve gait performance compared with standard continuous DBS. The adaptive system successfully synchronized stimulation with patient moment-to-moment neural activity and produced significant improvements in gait quality. Patients experienced fewer freezing episodes, smoother gait initiation, increased walking stability, and improved overall mobility. Importantly, stimulation was delivered only when required, reducing total stimulation time while maintaining or enhancing therapeutic benefit. The system was well tolerated, and no unexpected safety concerns were identified. These findings suggest that tailoring stimulation according to real-time brain activity can more effectively address the dynamic motor deficits characteristic of Parkinson's disease than fixed stimulation paradigms.

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