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Hematologic data predict survival in Mexican Mestizo people with Creutzfeldt-Jakob disease

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Abstract

Objective: *Creutzfeldt-Jakob disease (CJD) is a rare cause of rapidly progressive dementia due to the accumulation of misfolded prion proteins (PrPC) in the brain. Mortality is essentially universal within months to a few years after symptom onset. Here, we evaluated biomarkers derived from baseline complete blood counts (CBCs) in search of readily available predictors of disease progression using survival span as an outcome.* **Methods:** *We analyzed retrospective data derived from the baseline CBC from Mexican Mestizo individuals. We performed Spearman rho correlation to determine the association between survival time from disease onset with leukocyte and erythrocyte counts of people with CJD. We used Cox proportional hazard models to predict survival time, and log-rank tests to compare survival of subgroups.* **Results:** *We included 22 people with probable or definite CJD. Twelve (55%) were female. The mean age at diagnosis was 55 years (interquartile range: 25–85). Lower hemoglobin ($r = –0.494$, $p = 0.019$), hematocrit ($r = –0.445$, $p = 0.037$), and lymphocyte ($r = –0.421$, $p = 0.050$; log-rank test: $\chi^2 = 3.7$, $p = 0.05$) counts and higher neutrophils ($r = 0.404$, $p = 0.061$; log-rank test: $\chi^2 = 5.7$, $p = 0.02$) were associated with longer survival time.* **Conclusions:** *In the present study, we observed that common hematological values derived from a CBC were associated with survival span in people living with CJD. Those values support previous observations suggesting that the circulating availability of wild-type prion protein in blood cells is a limiting factor in the production of misfolded prion protein.*

Keywords: *Creutzfeldt-Jakob disease. Complete blood counts. Prion disease. Survival time. Biomarkers.*

Los datos hematológicos predicen la supervivencia en mestizos mexicanos con enfermedad de Creutzfeldt-Jakob

Resumen

Objetivo: *La enfermedad de Creutzfeldt-Jakob (ECJ) es una causa de demencia de rápida progresión debido a la acumulación de proteínas priónicas cerebrlaes mal plegadas. La mortalidad es prácticamente universal en un plazo de meses a pocos años tras el inicio de los síntomas. En este estudio evaluamos biomarcadores derivados de la biometría hemática (BH) basal buscando de predictores accesibles de progresión de ECJ, utilizando la supervivencia como desenlace.* **Métodos:** *Analizamos datos retrospectivos derivados de BH basal de individuos mestizos mexicanos con ECJ. Realizamos*

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una correlación rho de Spearman para determinar la asociación entre la supervivencia desde el inicio de síntomas y los recuentos de leucocitos y eritrocitos. Utilizamos modelos de riesgos proporcionales de Cox para predecir el tiempo de supervivencia y pruebas de log-rank para comparar la supervivencia de los subgrupos. **Resultados:** *Incluimos a 22 personas con ECJ probable o confirmada. Doce (55%) eran mujeres. La edad media al momento del diagnóstico fue de 55 años (RIC: 25-85). Un recuento bajo de hemoglobina (r = –0.494, p = 0.019), hematocrito (r = –0.445, p = 0.037) y linfocitos (r = –0.421, p = 0.050; prueba log-rank: χ^2 = 3.7, p = 0.05) y un recuento elevado de neutrófilos (r = 0.404, p = 0.061; prueba log-rank: χ^2 = 5.7, p = 0.02) se asociaron con una mayor supervivencia.* **Conclusiones:** *En el presente estudio observamos que los valores hematológicos comunes obtenidos a partir de la BH se asociaron con la supervivencia en personas con ECJ. Estos valores respaldan observaciones previas que sugieren que la disponibilidad circulante de la proteína priónica silvestre en las células sanguíneas puede ser un factor limitante en la producción de proteínas priónicas mal plegadas.*

Palabras clave: *Enfermedad de Creutzfeldt-Jakob. Hemograma completo. Enfermedad priónica. Tiempo de supervivencia. Biomarcadores.*

Introduction

Creutzfeldt-Jakob disease (CJD) is a rare pathology caused by misfolded (PrPSc) prion protein (PrPC), characterized by rapidly progressive dementia[1,2]. The median survival in white and Asian populations is about 1 year from the onset of symptoms[1,3,4]. A longer survival than the above-mentioned has been reported in people of Mexican ancestry[5]. A series of studies facilitate the diagnosis and progression of CJD; however, in low-and middle-income countries, most are not readily available[2,4]. The identification of low-cost, ubiquitous laboratory markers of disease progression is crucial. Here, we analyzed the correlation between biomarkers derived from the complete blood count (CBC), a readily available test, with survival rates in people with CJD in Mexico.

Materials and methods

We conducted an observational, cross-sectional study based on retrospectively collected data. For research purposes, dates were accessed in DD/MM/YYYY format. We reviewed data from a cohort of previously unpublished cases of CJD from two tertiary-care public institutions in Mexico City: Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán and Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, between January 1, 1990, and July 31, 2024. Inclusion criteria were all records obtained that had a diagnosis of probable CJD (1) rapidly progressive dementia; (2) the presence of at least two of the following: akinetic mutism, myoclonus, pyramidal or extrapyramidal signs, visual or cerebellar dysfunction; (3) 14-3-3 protein positivity; or (4) pathological electroencephalogram or pathological magnetic resonance imaging)] or definitive (genetically confirmed)[6]; likewise, complete clinical and paraclinical data were available, as well as accurate information on their evolution, and their follow-up had ended due to death or discharge from the institution. Exclusion criteria were those patients with a diagnosis of rapidly progressive dementia who did not meet sufficient criteria for a probable or definitive diagnosis of CJD, as well as those patients with a diagnosis of possible CJD[6]. Survival time was defined as the time elapsed from the onset of the first symptom (as defined above) to death or the last live report of the patient. For our objectives, as a baseline, we used the first blood sample collected after the onset of symptoms. Continuous variables are presented as median and interquartile range (IQR). Spearman's rho correlation analysis was performed to determine the associations between survival time and leukocyte and erythrocyte counts. All leukocyte and erythrocyte indices analyzed were binned in the median. Cox proportional hazard models were used to predict survival time, log-rank tests were applied to compare the survival of groups with low and high cell counts with respect to their medians. All statistical analyses were performed using R software, v. 4.3.2[7]. To minimize the risk of Type I error derived from the simultaneous analysis of multiple hematologic indices, we applied multiple comparison correction methods using the Bonferroni, Holm, and Benjamini-Hochberg procedures (data not shown). This study protocol was reviewed and approved by the Ethics in Research and Human Research Committees of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, with approval number ID: NER-5277-24-26-1. Due to the retrospective nature of the study, a waiver for informed consent was granted.

Results

We analyzed baseline hematologic data from 22 people with probable or confirmed CJD; 12 (55%) were

Table 1. Leukocyte and erythrocyte indices from people with CJD in Mexico

Leukocyte/erythrocyte index	Sample, total n	Median	IQR	Range	Correlation with survival time, r	p
Leukocytes (K/uL)	22	8.35	6.44-9.40	2.88-14.50	–0.051	0.819
Erythrocytes (M/uL)	22	4.87	4.56-5.29	3.29-8.70	–0.073	0.743
Hemoglobin (g/dL)	22	14.85	13.05-15.75	10.40-17.60	–0.494	0.019
Hematocrit (%)	22	44.80	39.65-46.75	30.00-50.50	–0.445	0.037
MCV (fL)	22	90.25	88.02-92.42	61.00-97.60	+0.197	0.378
MCH (pg)	22	30.25	30.00-31.25	25.90-34.30	+0.096	0.670
MCHC (%)	22	33.60	33.00-34.37	28.70-36.70	–0.073	0.746
Platelets (K/uL)	22	250.50	183.25-302.00	107.00-406.00	+0.311	0.158
Lymphocytes (%)	22	22.55	15.45-33.42	4.00-53.40	–0.421	0.050
Monocytes (%)	22	8.75	6.37-9.57	2.50-13.80	–0.221	0.320
Neutrophils (%)	22	68.80	52.77-75.00	29.40-86.90	+0.404	0.061
Eosinophils (%)	22	1.75	1.35-2.62	0.40-9.70	–0.050	0.823
Basophiles (%)	22	0.45	0.40-0.70	0-1.20	+0.053	0.811

MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration, CJD: Creutzfeldt-Jakob disease.

female. One subject was categorized as definite CJD, confirmed genetically, while 21 people met the criteria for probable CJD. The mean age at diagnosis was 55 years (IQR: 25-85, median: 59 years). The median survival of the cohort was 187 days. The mean survival of the cohort was 257 days. One-year survival rate was 32% (7/22). Descriptive statistics for all leukocyte and erythrocyte index values analyzed are shown in table 1. Lower hemoglobin (Hb) (subgroup median = 13 g/dL, range: 10.4 g/dL-14.8 g/dL, r = –0.494, p = 0.019; log-rank test: $\chi^2 = 0.9$, p = 0.3), hematocrit (HCT) (subgroup median = 39.3%, range: 30.0-44.5%, r = –0.445, p = 0.037; log-rank test: $\chi^2 = 0.6$, p = 0.4), and lymphocyte (subgroup median = 15.3%, range: 4.0%-21.5%, r = –0.421, p = 0.050; log-rank test: $\chi^2 = 3.7$, p = 0.05) counts, and higher baseline neutrophils (subgroup median = 75.6%, range: 69.7-86.9%, r = 0.404, p = 0.061; log-rank test: $\chi^2 = 5.7$, p = 0.02), were associated with longer survival time (Fig. 1), with a 10-month survival rate of 59% in individuals who met these parameters. After application of the aforementioned methods of correction for comparisons, none of the hematological indices described in table 1 reached statistical significance at the adjusted level (p < 0.05); however, the data corresponding to Hb, HCT, Lymphocytes, and Neutrophils presented the lowest adjusted p values through the Benjamini-Hochberg method (p = 0.198). The neutrophil-to-lymphocyte ratio, calculated as the absolute neutrophil count divided by the absolute lymphocyte count[8], did not correlate with survival span. Similarly, in this cohort, the monocyte-to-lymphocyte and the lymphocyte-to-platelet ratios did not correlate with survival span in CJD (data not shown).

Discussion

Here, we evaluated the association between the survival of Mexican people with CJD and the values obtained for the CBC. In the analyzed population, we observed a strong correlation between lower Hb and HCT values with longer survival, which concurs with observations in Chinese populations[1]. While our study is not designed to address causality, this may be due to the interaction of Hemin-PrPC, which promotes the increase of Hb synthesis in the erythropoietic pool[9]. Thus, the neurologic damage induced by PrPSc at the brain level can be interpreted as proportional to Hb and HCT counts[9]. On the other hand, we also observed a possible association between leukocyte counts and survival, probably attributed to PrPC located in peripheral blood CD34+ hematopoietic progenitor cells functioning as a cell receptor and precursor of PrPSc. Hematopoietic stem cells strongly express PrPC, with clear

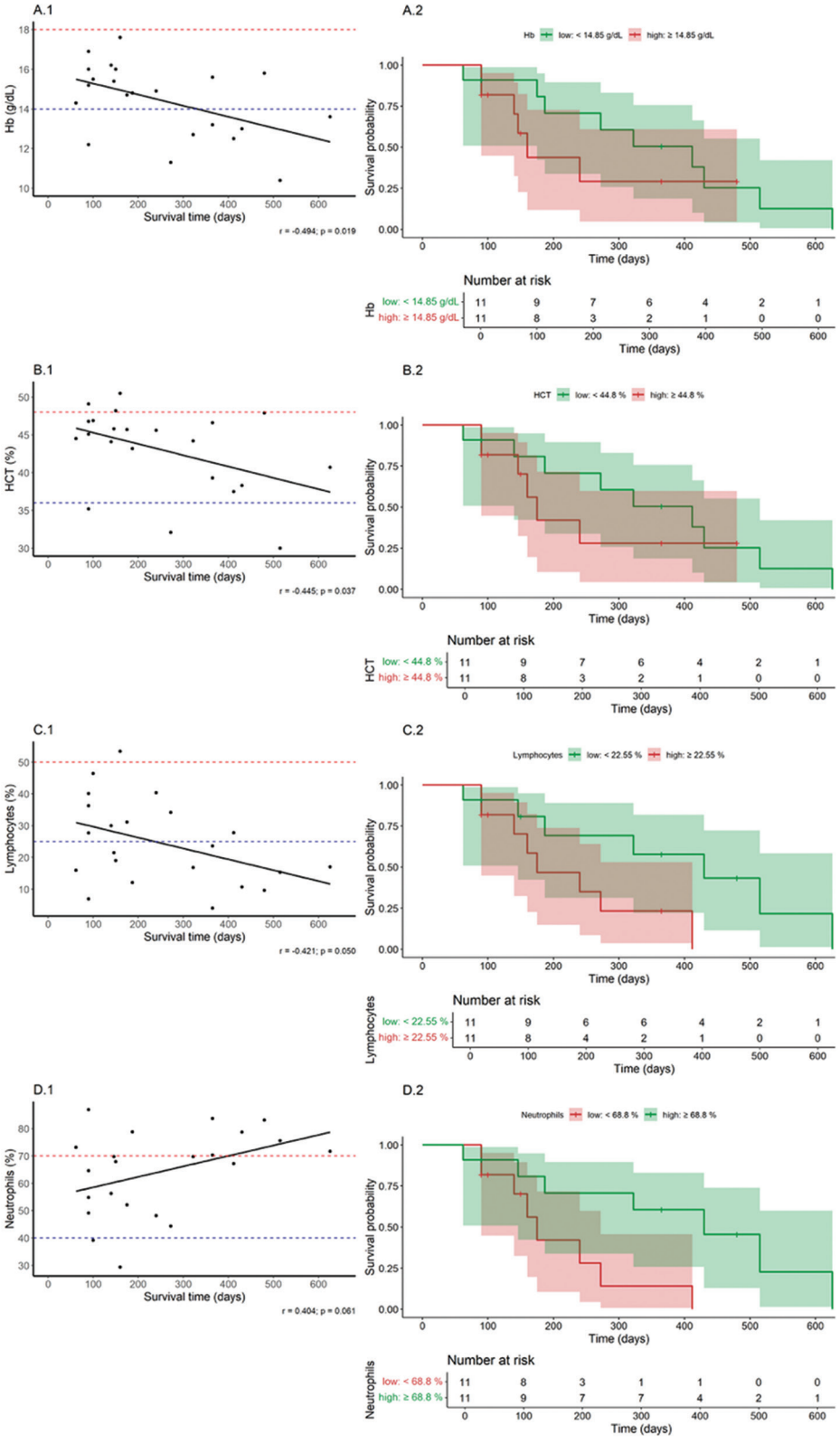

Figure 1. Association between survival time and leukocyte and erythrocyte abnormalities (X.1 – left figure: blue and red lines represent the lower and upper values, respectively, of the reference parameters used); and survival analyses with Cox proportional hazard models (X.2 – right figure) levels in people with Creutzfeldt-Jakob disease in Mexico. Hemoglobin (**A.1**, **A.2**), HCT (**B.1**, **B.2**), lymphocytes (**C.1**, **C.2**), and neutrophils (**D.1**, **D.2**).

lineage variability. During differentiation, the granulocytic lineage down-regulates PrPC, while PrPC expression is maintained in lymphoid lineages throughout the lifespan of the lymphocyte[10]. Hence, the granulocytic lineage expresses lower levels of PrPC in comparison to the lymphocytic lineage[11]. In our cohort, low levels of lymphocytes and high levels of neutrophils were associated with longer survival; as PrPC expression is needed to produce the misfolded (PrPSc) protein, we speculate that a shift to higher circulating numbers of low-PrPC-expressing granulocytes (and concomitant reduction in high-PrPC-expressing circulating monocytes) decreases the available pool of the PrPC needed as seed for PrPSc formation[12-14]. Our Hb and HCT observations are in agreement with previous reports[1]; however, we also observed that leukocyte markers predict survival span, something not previously observed. This may be due to genetic variability but also because our cohort is more female-tilted and younger than those in other studies[1].

This study has some limitations. First, we included a small number of people, which represents a possible limitation in terms of statistical power, by decreasing the ability to identify true associations. This limitation is reflected in the presence of trends that, although they do not reach statistical significance after the application of corrections for multiple comparisons, suggest possible relevant biological relationships; this is due in part to the rarity of CJD, but we also suspect that in Mexico, CJD is underdiagnosed due to a combination of a lack of familiarity with a rare disorder, with limited access to tertiary care in people with lower socioeconomic status, and those living far from tertiary care institutions. Furthermore, all cases are derived from only two institutions, potentially biasing the analysis due to geographic or financial constrictions. In addition, survival by subtype classification is not assessed for this cohort, since only one patient with a genetic diagnosis is reported. Our results are, in many ways, preliminary and will need to be replicated and validated in independent cohorts, and with a larger sample size. Nevertheless, these findings constitute a valuable starting point, as they represent the first Mexican pilot study focused on the analysis of hematological parameters and their possible correlation with the underlying pathophysiological mechanisms in prion diseases.

Conclusions

Our data indicate that certain parameters obtained in a routine baseline CBC, an inexpensive and ubiquitous blood test, can be useful in estimating the survival span of people with CJD.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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