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SHORT COMMUNICATION

Impact of the COVID-19 pandemic on Creutzfeldt–Jakob disease surveillance and patient care in the United Kingdom

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Abstract

Background and purpose: Creutzfeldt–Jakob disease (CJD) is lethal and transmissible. We assessed the impact of the COVID-19 pandemic on UK CJD surveillance. We hypothesized that (i) disruptions prolonged diagnostic latency; (ii) autopsy rates declined; and (iii) COVID-19 infection negatively affected diagnosis, care, and survival.

Methods: We retrospectively investigated the first year of the pandemic, using the preceding year as a comparator, quantifying numbers of individuals assessed by the UK National CJD Research & Surveillance Unit for suspected CJD, time to diagnosis, disease duration, and autopsy rates. We evaluated the impact of COVID-19 status on diagnosis, care, and survival in CJD.

Results: A total of 148 individuals were diagnosed with CJD in the pandemic (from a total of 166 individuals assessed) compared to 141 in the comparator (from 145 assessed). No differences were identified in disease duration or time to diagnosis. Autopsy rates were unchanged. Twenty individuals had COVID-19; 60% were symptomatic, and 10% had severe disease. Disruptions in diagnosis and care were frequently identified. Forty percent of COVID-19-positive individuals died; however, COVID-19 status did not significantly alter survival duration in CJD.

Conclusions: The COVID-19 pandemic has not impacted UK CJD case ascertainment or survival, but diagnostic evaluation and clinical care of individuals have been affected.

KEYWORDS
CJD, dementia, infectious diseases, neurodegenerative, prion

INTRODUCTION

Creutzfeldt–Jakob disease (CJD) is rapidly progressive, lethal, and transmissible [1]. CJD surveillance is an essential public health activity, and programmes operate globally aiming for accurate case ascertainment and mitigation of transmission. The UK National CJD Research & Surveillance Unit (NCJDRSU) delivers comprehensive surveillance, undertaking direct clinical assessments in all individuals suspected to have CJD. The NCJDRSU also delivers cerebrospinal fluid (CSF) diagnostic analysis, and specialist neuroimaging and neuropathology expertise.

The impact of the COVID-19 pandemic on CJD surveillance and patient care has not been previously reported. The NCJDRSU has remained active throughout the pandemic, delivering the majority of assessments via telehealth [2]. We report on the impact of the COVID-19 pandemic on UK CJD surveillance and patient care. We hypothesized that (i) health care disruptions prolonged time to diagnosis; (ii) COVID-19 infection impacted negatively on CJD

diagnosis, care, and survival duration; and (iii) the pandemic led to decreased autopsy rates.

METHODS

Data were obtained from the NCJDRSU database. We defined the 12-month period from 1 March 2020 as the pandemic period, with the preceding 12-month period used as a comparator. We quantified referrals in each period, the number of individuals directly assessed for suspected CJD, including demographic data, disease duration, time to diagnosis, diagnostic classification according to criteria [3], and autopsy rates.

We identified all individuals with laboratory-confirmed COVID-19 and compared demographics, survival duration, and time to diagnosis with individuals without COVID-19. We estimated site of exposure based on location in the 14 days prior to detected COVID-19, and documented symptom presence, infection severity, and outcome (death or recovery). We measured disruptions in diagnostic workup, such as delays or barriers to neurologist assessment and investigations, and to discharge timing.

Statistical analysis was performed using R. Age, duration, and categorical variables were treated with the independent samples *t*-test, Mann–Whitney *U*-test, and chi-squared tests, respectively. Survival analysis was performed using the Kaplan–Meier estimator.

RESULTS

A total of 807 individuals were referred to the NCJDRSU during the study period (401 during the pandemic, 406 during the comparator period) and underwent investigation for CJD; 166 (41.4%) of those referred during the pandemic had high likelihood of CJD and were directly assessed by NCJDRSU clinicians, compared to 145 (35.7%) in the comparator period. There were no demographic differences between cohorts (Table 1). A total of 148 (89.1%) individuals were diagnosed with CJD during the pandemic, compared to 141 (97.2%) in the comparator period. There were no statistically significant differences in time to diagnosis and overall survival between periods (Table 1, Figure 1a). The remainder of individuals assessed received alternative diagnoses, including dementia with Lewy bodies (DLB), vascular dementia, psychiatric disorders, and steroid-responsive encephalopathy. At the time of analysis (12 May 2021), 34 (20.5%) and 11 (7.6%) individuals remained alive in the pandemic and comparator cohorts, respectively.

Twenty (6.4%) individuals had laboratory-confirmed COVID-19. No differences were observed between these individuals and COVID-19-negative individuals in age (68.5 vs. 68.7 years, $p = 0.89$), sex (40% vs. 51.2% males, $p = 0.46$), or race (94.7% vs. 90.2% White, 5% vs. 8.2% non-White, 5% vs. 15.8% missing data, $p > 0.99$). Seventeen (85%) were assessed during the pandemic. The remaining three (15%) were assessed in the comparator period; all three had prolonged survival (464 days in one deceased individual; two remained alive at the time of analysis), acquiring COVID-19 in care homes.

TABLE 1 National CJD Research & Surveillance Unit activity in the 12-month period before and during the pandemic

	Prepandemic	Pandemic	*p*
Enquiries	406	401	
Visited, *n* (%)	145 (35.7%)	166 (41.4%)	
Age (years) ± SD	69.0 ± 10.1	68.5 ± 11.3	0.7
Male, *n* (%)	78 (53.8%)	79 (47.6%)	0.33
Deceased, *n* (%)	134 (92.4%)	132 (79.5%)	
Post-mortem, *n* (%)	17 (12.7%)	12 (9.1%)	0.46
CJD, *n* (% visited)	141 (97.2%)	147 (88.6%)	
Classification, *n* (%)			
Possible	3 (2.1%)	6 (4.1%)	
Probable	128 (90.8%)	131 (89.1%)	
Definite	10 (7.1%)	10 (4.1%)	
CJD subtype, *n* (%)			
Sporadic	132 (93.6%)	142 (96.6%)	
VPSPr	1 (0.7%)	1 (0.7%)	
Genetic	8 (5.7%)	3 (2.0%)	
Iatrogenic	0	1 (0.7%)	
Survival post-diagnosis (IQR)	16 (8–37)	13 (7–30)	0.18
Time to CJD diagnosis (IQR)	109 (56–211)	88(55–178.5)	0.32

Note: Age is shown as mean in years; survival post-diagnosis and time to diagnosis are shown as median in days. Post-mortem percentage uses deceased count as denominator.

Abbreviations: CJD, Creutzfeldt–Jakob disease; IQR, interquartile range; VPSPr, variably protease-sensitive prionopathy.

Five (25%) individuals acquired COVID-19 in the community (preceding CJD symptoms by several weeks in two), 10 (50%) in hospital, and five (25%) in care homes (of whom four recovered and one died). Twelve (60%) had symptoms including cough, fever, and requirement for supplementary oxygen. Two (10%) had severe COVID-19; one required high-flow oxygen, and one required invasive ventilation. Eight (40%) died during the infection, of whom seven were symptomatic.

Thirteen individuals had COVID-19 during the diagnostic workup. Disruptions in diagnosis included delayed neurology assessment (two, 15.4%) and lumbar puncture (LP; eight, 61.5%; four ultimately not performed due to patient death). Real-time quaking-induced conversion (RT-QuIC) analysis was not undertaken in two (15.3%) individuals early in the pandemic, as health and safety risk assessments relating to potential generation of aerosols containing SARS-CoV-2 were unavailable. As scientific evidence became available regarding the lack of SARS-CoV-2 in CSF of COVID-19 patients [4], RT-QuIC analysis was resumed. Ten (76.9%) individuals underwent magnetic resonance imaging (MRI). Three (23.1%) died without any investigations; one was diagnosed with DLB, and two had autopsies. Of these, one had confirmed sporadic CJD (sCJD), and prion disease was excluded in the other. Seven (53.8%) died with

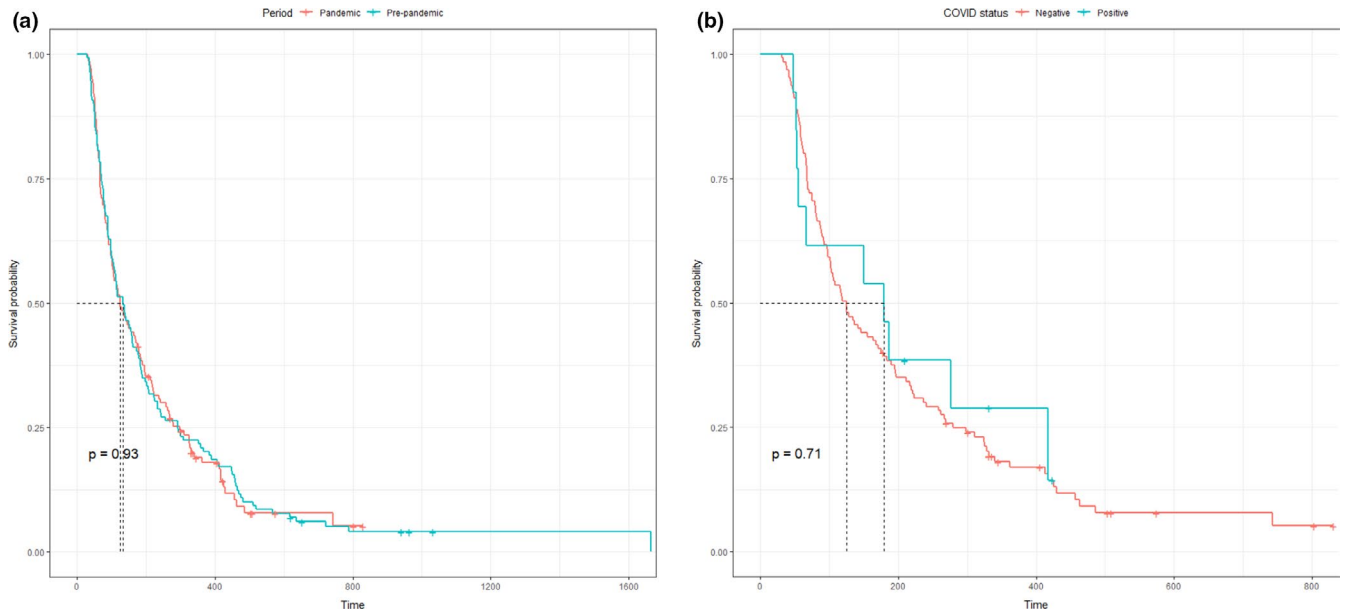

FIGURE 1 (a) Survival (days) in individuals with definite or probable Creutzfeldt–Jakob disease (CJD), pandemic versus prior 12 months. (b) Survival (days) in individuals with definite or probable CJD grouped by COVID-19 status; data are from individuals assessed during the pandemic phase [Colour figure can be viewed at wileyonlinelibrary.com]

COVID-19, whereas six (46.2%) recovered; discharge was delayed in three (23.1%), whereas two (15.4%) experienced no delays, and one (7.7%) died from CJD in hospital. Median time to diagnosis in COVID-19-infected individuals was prolonged (139.5 days, interquartile range [IQR] = 55–208.2]) compared to unaffected individuals (95, IQR = 56–191); this difference was not significant ($p = 0.53$).

The final diagnosis was CJD in 18 (90%) individuals with COVID-19. One (5%) fulfilled criteria for definite sCJD, 15 (75%) for probable sCJD, and two (10%) for possible sCJD. One (5%) had DLB, and one (5%) had autopsy-confirmed cerebrovascular disease.

Survival was assessed in definite/probable CJD cases grouped by COVID-19 status. No difference was observed (median survival = 179 days in COVID-19-positive patients vs. 125 days in COVID-19-negative patients, $p = 0.75$; Figure 1b). Significant pandemic-related challenges were present irrespective of COVID-19 status, including limited contact with relatives at all times.

Autopsy rates during the pandemic (12, 9.1%) were unchanged from the comparator period (17, 12.7%; $p = 0.46$; Table 1).

DISCUSSION

The NCJDRSU maintained national CJD surveillance amid the pandemic, despite challenges including travel restrictions [2] and regional disruptions in services. Referral numbers were unchanged, and time to diagnosis was unaffected. With typical time to diagnosis of 2–3 months and survival post-diagnosis of only several weeks, rapid diagnosis is essential to optimize care, exclude reversible mimics [5], and minimize transmission [6].

CJD typically presents with rapidly-progressive dementia [1], and histories rely on informants. Disrupted contact between patients and their networks presented frequent challenges to diagnosis and care. Although this study was not designed to quantify associated human costs, patients' relatives frequently lamented the challenges they experienced.

The NCJDRSU assessed a higher number of individuals during the pandemic, with 8.1% fewer receiving a diagnosis of CJD. This reflects implementation of telehealth [2], enabling timely assessments. Assessing individuals with alternative conditions is valuable: differentiation from CJD can be challenging; likewise, CJD can mimic other diseases [7]. Our previous work has demonstrated the utility of telehealth for robust, timely CJD surveillance [2].

In individuals with COVID-19, time to diagnosis was not statistically significantly prolonged. However, disruptions in diagnostic tests were frequent. Factors included requirements for isolation facilities, staffing shortages, severe COVID-19, and delaying LP until recovery to allow RT-QuIC testing. Most individuals underwent MRI, enabling timely diagnosis [8]. Other challenges included disruptions in care continuity and local neurology input. These also affected many individuals without COVID-19.

The case fatality rate (CFR) from COVID-19 of 40% in our series is high compared to overall rates of around 2% [9]. Neurodegenerative disorders carry heightened mortality from COVID-19 [10,11]. Individuals hospitalized with CJD generally have advanced disease, with significant disability and poor physiological reserve, implying heightened COVID-19 mortality. The prognosis in CJD is poor, and in this series, it is difficult to differentiate between (i) individuals in whom COVID-19 shortened survival and (ii) individuals dying from CJD. COVID-19 did not alter survival. Regardless, the high CFR demonstrates the importance of minimizing COVID-19 exposure in CJD.

A relationship between COVID-19-related inflammation and accelerated neurodegeneration in CJD has been previously hypothesized [12]. Survival data from our study do not suggest such an association, but future prospective studies may be warranted.

Although Black and minority ethnic individuals have increased risks of COVID-19 infection and mortality [13], we observed no demographic differences between individuals grouped by COVID-19 status; however, this study is likely underpowered to detect any differences in race or ethnicity among CJD patients with COVID-19.

Despite autopsy service restrictions in many regional centres, there was no significant reduction in overall national autopsy rates. Autopsies have declined over the past decade of UK surveillance [14], underscoring the imperative of in-life diagnosis with minimal disruptions and delays.

Strengths of this study include comprehensive assessment of a 2-year national cohort. By combining direct assessments with dedicated biomarker, neuroradiology, and neuropathology expertise, the NCJDRSU is able to accurately ascertain and diagnostically classify individuals with CJD. This is reflected in the numbers of cases of probable/definite CJD identified in our study, part of a long-term trend of increasing ascertainment in the UK [15]. Longitudinal follow-up allows determination of disease duration and identification of complications including COVID-19 infection. Our methodology maximizes case ascertainment, minimizes selection bias, allows maximally accurate classification, and provides detailed clinical and longitudinal information.

This study has some limitations. Widespread COVID-19 testing among hospitalized individuals occurred in the UK, but rates of community testing were variable, although these vastly increased during the study period. With high rates of asymptomatic COVID-19 [16,17], underascertainment may have been present, particularly outside the hospital. We defined the pandemic onset as 1 March 2020 based on reported COVID-19 rates, which were minimal before this [18]. However, true rates in earlier weeks will have been higher than reported owing to limited testing and frequent mild/asymptomatic infections. Lastly, we did not analyse socioeconomic status, known to influence COVID-19 risk and mortality [19].

In conclusion, this is the first study demonstrating the impact of the pandemic on national CJD surveillance and care. We demonstrated stable referral and case numbers, and no effects on survival duration, time to diagnosis, or autopsy rates. We quantified COVID-19 infections and demonstrated multiple barriers to diagnosis and care in affected individuals, a CFR of 40%, and no effect on survival duration. Prevention of COVID-19 is essential to optimize diagnosis and care in CJD. CJD surveillance is an essential public health activity and must persist amid competing crises.

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CONFLICT OF INTEREST

None to disclose.

AUTHOR CONTRIBUTIONS

Neil Watson: Conceptualization (lead), data curation (lead), formal analysis (lead), investigation (equal), methodology (lead), project administration (lead), visualization (equal), writing–original draft (lead), writing–review & editing (equal). **Jack Kirby:** Investigation (supporting), methodology (supporting), project administration (supporting), writing–review & editing (supporting). **Hatice Kurudzhu:** Investigation (supporting), methodology (supporting), project administration (supporting), writing–review & editing (supporting). **Margaret Leitch:** Writing–review & editing (supporting). **Janet MacKenzie:** Data curation (lead), project administration (supporting), resources (lead), writing–review & editing (supporting). **Blaire Smith-Bathgate:** Writing–review & editing (supporting). **Colin Smith:** Supervision (supporting), writing–review & editing (supporting). **David Summers:** Writing–review & editing (supporting). **Alison J. E. Green:** Writing–review & editing (supporting). **Suvankar Pal:** Conceptualization (lead), formal analysis (supporting), investigation (equal), methodology (equal), supervision (lead), visualization (equal), writing–original draft (supporting), writing–review & editing (equal).

ETHICAL APPROVAL

South East Scotland Research Ethics Service has approved NCJDRSU activity as essential for public health (reference NR/162AB13, 2016).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author (S.P.). The data are not publicly available due to restrictions (e.g., they contain information that could compromise the privacy of research participants).

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