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Epilepsy diagnosis after Covid-19: A population-wide study

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ABSTRACT

Background: We aimed to investigate whether SARS-CoV-2 infection was associated with an increased risk of incident epilepsy.

Methods: National register-based matched study. Verified cases of SARS-CoV-2 infection were acquired from the system for communicable disease surveillance in Sweden (SmiNet) and linked to data from the National Patient Register (NPR) and Cause of Death register in Sweden. Cases and non-infected controls were compared using a Cox proportional hazards model.

Results: A total of 1,221,801 SARS-CoV-2 infected patients and 1,223,312 controls were included. Infection was not associated with an increased risk of epilepsy on a whole population level (HR 1.01, 95% CI 0.92–1.12). Statistically significant effects were observed in patients between 61 and 80 years (HR 1.66, 95% CI 1.37–2.02), also when adjusting for stroke, traumatic brain injury, tumours (same age group HR 1.50, 95% CI 1.24–1.82) and mechanical ventilation (HR 1.28, 95% CI 1.05–1.57). In patients 81–100 years, a similar significant difference was observed (HR 1.77, 95% CI 1.30–2.42), which remained after adjustment for stroke, traumatic brain injury and tumours (HR 1.51, 95% CI 1.10–2.05) but not when mechanical ventilation was included as a covariate (HR 1.34, 95% CI 0.97–1.84).

Conclusions: On a whole population level, SARS-CoV-2 infections is not associated with an increased risk of epilepsy. In patients above 60 years, a moderately increased risk of epilepsy was observed. However, considering potential non-controllable bias and that Covid-19 patients in intensive care present with a lower risk than the general ICU population, the virus-induced epileptogenic effect is likely very small.

1. Introduction

Whether SARS-CoV-2 infects, and how it affects, the central nervous system (CNS) in the acute phase of disease has been an issue of research and discussion during the Covid-19 pandemic. The virus does not appear to be highly neurotropic or neuroinvasive, although rare cases of SARS-CoV-2 related encephalitis have been described [1].

Early reports described a substantial proportion of hospitalized patients showing affected level of consciousness, and patients in need of intensive care often presents with increased levels of brain injury biomarkers in cerebrospinal fluid, indicating axonal injury [2]. Specific engagement of the olfactory system appears relatively common, causing anosmia in a majority of patients, and changes in corresponding parts of the brain has been described [3]. Further, neurocognitive impairment is part of the complex syndrome of post-infectious disease called long

covid [4]. Case reports of patients with positive SARS-CoV-2 PCR in cerebrospinal fluid (CSF) has been described, but the current consensus is that the virus does not readily infect the brain and that most CNS symptoms are mediated through immunological or metabolic mechanisms [5].

There are case reports and retrospective studies describing onset of seizures and epilepsy in conjunction with SARS-CoV-2 [6–10], but in total the literature points to acute symptomatic seizures being relatively rare and chance-associations with epilepsy-onset being hard to exclude [11]. We have previously shown that patients suffer an increased risk of epilepsy following both bacterial and viral CNS infections, most prominently after herpes simplex encephalitis and brain abscesses which can both cause loss of brain tissue and cortical scarring [12]. The objective of this study was to investigate whether the less virulent but far more common SARS-CoV-2 infection could also increase risk of epilepsy.

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2. Methods

2.1. Study outline

This was a national register-based study. All individuals with a positive laboratory test for SmiNET (PCR or antigen) were considered exposed. To identify a covid-free representative cohort, Statistics Sweden identified one control per exposed matched for sex and age on 1 March 2016, before the pandemic. Cases could not be controls and controls could only be drawn once.

SmiNET identified 1237,381 individuals with a positive test between 4 Feb 2020 and 16 Dec 2021. Controls could not be found for 718 exposed that were not in the population register on their test day, and 245 individuals with possible registration errors. Individuals with a registration code for epilepsy in the national patient register (NPR) before their index date (13,636 exposed and 13,332 controls, 1.1%) were also excluded. The final cohorts consisted of 1221,801 exposed and 1223,312 controls.

2.2. Registry data collection

Based in the unique civic registration number of all Swedish individuals, data on epilepsy, comorbidities and survival were collected from the comprehensive Swedish health registers. The National Patient Register (NPR) contains all ICD-10 codes and dates of out- or inpatient hospital-based care in Sweden during the study period. The Cause of Death register contains all dates of death for individuals in Sweden. All registers were cross-referenced by the register holders and the dataset was anonymized before we were given access to it.

Epilepsy was defined as occurrence of ICD-code G40 in the NPR, seizure was defined as occurrence of R568, and status epilepticus as G41. Based on relevant ICD-codes, we identified stroke (I61, I62, I63, I69), traumatic brain injury (TBI, S01-S06, S209), brain tumor (C71, C793, D430, D330, D32), Covid-19 (U071), and procedures related to mechanical ventilation/tracheostomy (procedure codes DG02, DG016, DG018). For TBI we used only admissions; for stroke and tumours both admissions and outpatient visits were used.

2.3. Statistical analysis

As index date, we used the day of the positive test for exposed, who were followed until the end of 2021. Index date for controls was 1 March 2016, and they were followed until the end of 2017. For incidence of epilepsy, we calculated the number of epilepsy cases per 100,000 person-years after index date until the last follow-up date.

The risk of epilepsy was estimated using Cox regression with a positive Covid-19 test as the covariate of interest. Event was the first occurrence of a diagnosis of epilepsy in the NPR. Participants were censored at death or last follow-up date. In an adjusted model, we included stroke, TBI, and brain tumor as time-updated covariates. In a second adjusted model, mechanical ventilation was added as a further covariate. The incidence was visualized with Kaplan-Meier curves. All analyses were performed in SPSS® version 28 (IBM, Armonk, NY).

2.4. Ethics

The study was approved by the Swedish Ethical Review Authority (permission number 2020–06378). The detailed register data is protected by Swedish privacy laws and an agreement with the National Board of Health and Welfare and cannot be shared by the authors.

3. Results

Demographically, the case and control groups were well matched for age and sex (Table 1). The dominating age groups were 21–60. Comorbidities were more common in the Covid-19 group than in

Table 1

Cohort characteristics. TBI=traumatic brain injury.

	Covid-19		Controls	
	n	%	n	%
Sex				
Male	599,313	49.0%	599,583	49.0%
Female	623,488	50.9%	623,729	51.0%
Age				
–20	240,230	19.6%	240,031	19.6%
21 - 40	421,202	34.4%	421,084	34.4%
41 - 60	400,364	32.7%	400,052	32.7%
61 - 80	127,501	10.4%	128,187	10.5%
81 - 100	33,290	2.7%	33,743	2.8%
100-	214	0.0%	215	0.0%
Comorbidities				
Stroke	19,190	1.6%	17,808	1.5%
TBI	45,505	3.7%	42,090	3.4%
Tumour	1012	0.1%	1122	0.1%
Mechanical ventilation	20,414	1.7%	2613	0.2%
Death	22,287	1.8%	14,380	1.2%

controls. It was much more common to have received mechanical ventilation among exposed and a greater proportion of individuals with a Covid-19-positive test had died at the end of follow-up.

3.1. Epilepsy incidence

A total of 639 exposed (0.05%) and 1255 controls (0.10%) developed epilepsy after the index date, with an incidence of 62 cases/100,000 patient years in exposed and 56 cases/100,000 patient years in controls (Table 2). Per age group, the incidence of epilepsy was lower than that seen in controls for individuals with a positive Covid-19 test in the age groups 21–40 and 41–60, but higher than controls for age groups 61–80 and 81–100 (Fig. 1).

3.2. Risk of epilepsy

In an overall Cox regression model, belonging to the group with positive Covid-19 test was not associated with an increased risk of epilepsy (HR 1.01, 95% CI 0.91–1.12). When stratified by age (Table 3), a positive Covid-19 test was associated with a decreased risk of epilepsy in age groups 21–40 and 41–60, and increased risk of epilepsy in age groups 61–80 and 81–100. When the analysis was adjusted for comorbidities, the HR of epilepsy was reduced. If mechanical ventilation was also included as a covariate, the HR associated with Covid-19 was further reduced but still statistically significant for ages 61–80, but no longer significant for ages 81–100. Judging by the slope of Kaplan-Meier curves, the increased risk of epilepsy in the older age groups was mainly caused by higher risk in close relation to the positive test (Fig. 2).

3.3. Mechanical ventilation

Given the effect of mechanical ventilation on HR of epilepsy, we assessed incidence for individuals receiving mechanical ventilation. The incidence of epilepsy for patients with an admission with both mechanical ventilation and simultaneous diagnosis of Covid-19 was 352 per 100,000 person years. For comparison, the incidence of epilepsy among individuals with mechanical ventilation for any reason was 532 per 100,000 person years among exposed and 1145 per 100,000 person years among controls.

4. Discussion

The totality of data suggests that Covid-19, compared to other brain infections, is not particularly prone to cause epilepsy, at least not of a magnitude detectable at the whole population level. The overall incidence of epilepsy was very similar in those with a positive covid test and

Table 2
Incidence of epilepsy after cohort entry. P-y = person years.

	Covid-19			Controls		
	n	P-y	n/100,000 years	n	P-y	n/100,000 years
All	639	1024,721	62	1255	2232,283	56
Male sex	339	495,017	68	659	1094,189	60
Women	300	529,704	57	596	1138,094	52
Age						
0 - 20	94	175,270	54	257	440,520	58
21 - 40	101	364,546	28	285	772,497	37
41 - 60	135	351,178	38	352	732,751	48
61 - 80	227	110,127	191	263	232,014	113
81 - 100	82	23,490	349	98	54,256	181
101+	0	111	0	0	243	0

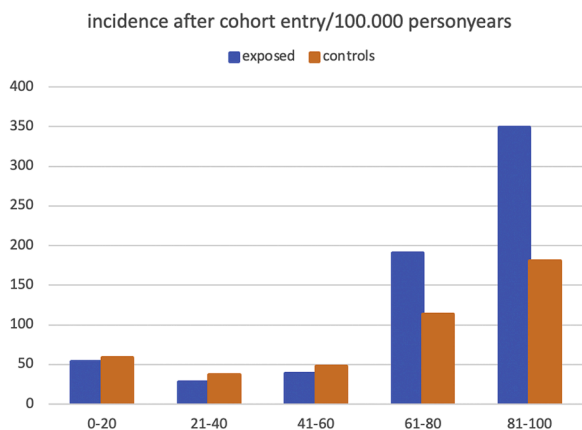


Fig. 1. Incidence of epilepsy after cohort entry per 100,000 person years, comparing Covid-19 exposed subjects and non-infected controls.

Table 3
Hazard ratio (HR) for epilepsy in different age groups by Cox regression. * Adjusted for stroke, traumatic brain injury (TBI), tumor. # Adjusted for stroke, TBI, tumor and mechanical ventilation.

Age	Unadjusted		Adjusted*		Adjusted#	
	HR	95% CI	HR	95% CI	HR	95% CI
0 - 20	0.84	0.65–1.09	0.84	0.65–1.08	0.80	0.62–1.04
21 - 40	0.63	0.49–0.80	0.62	0.49–0.79	0.59	0.46–0.75
41 - 60	0.78	0.63–0.97	0.80	0.65–0.99	0.65	0.52–0.81
61 - 80	1.66	1.37–2.02	1.50	1.24–1.82	1.28	1.05–1.57
81 - 100	1.77	1.30–2.42	1.51	1.10–2.05	1.34	0.97–1.84

controls. When data were stratified for age, the picture was somewhat nuanced, showing a lower incidence after Covid-19 in younger age groups and a higher incidence after Covid-19 in the elderly. The differences were however small and could very well represent different indications and incentives for testing depending on age.

In Sweden, testing for SARS-CoV-2 was widely available and, in many situations, a negative test allowed earlier return to work or education. In the age-groups of working life age, there may therefore well be

a “healthy tester” effect, meaning that healthy individuals are likely to be overrepresented among those obtaining a test. The test population under age 60 may therefore be healthier than the cross-section of the population represented in the control group. In addition, testing was ubiquitous in the health services, and all individuals admitted to hospital were tested. There will therefore be an association between a positive test and admission for any reason, which could have resulted in the higher risk of epilepsy seen in the older age groups. Indeed, Kaplan-Meier curves indicated that the increased risk in this age group was temporally closely related to the positive test. Markers of hospitalization and severe disease – illustrated by higher rates of mechanical ventilation and death - were more common in the cohort with Covid-19.

In the Cox regression model, we could not find an increased risk of epilepsy overall. The age groups showed risks in keeping with the incidence results. Interestingly, when the model was adjusted for comorbidities and ventilation, the increased HRs in older age groups were altered towards 1.0 – indicating that confounding by comorbidities could be partly responsible for the increased risk observed for SARS-CoV-2 positive patients.

Need of respiratory support was a clear risk factor of subsequent epilepsy, both before and during the onset of the SARS-CoV-2 pandemic. The highest incidence was seen in the control population, in patients that were admitted with mechanical ventilation before the pandemic. This risk exceeded the risk of patients with Covid-19 admitted during the pandemic, indicating that Covid-19 patients receiving intensive care actually have a lower risk of developing epilepsy than other ICU patients. This is not surprising, since the comparison is in effect one between patients with intensive care for a primarily respiratory problem and patients with intensive care for a wide range of severe medical conditions including those affecting the brain.

Importantly, our results should not be interpreted as evidence that Covid-19 can never cause epilepsy. There is an emerging body of literature suggesting that severe Covid-19 can cause brain damage, via stroke, metabolic deregulation or immunologic mechanism that are not yet fully elucidated [11,13]. All brain-injuring processes can cause epilepsy, so in individual cases cortical or large brain lesions may well be epileptogenic. Also, it is important to stress the short-term nature of the data available. The risk of epilepsy is highest soon after brain lesions, but a slightly elevated risk persists for extended periods of time after CNS infections or trauma [12,14–16]. Similar long-term effects of Covid are

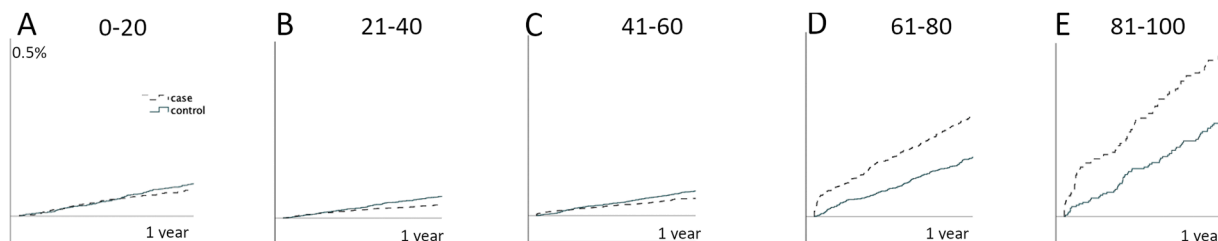


Fig. 2. Kaplan-Meier curves of epilepsy in the different age groups, compared to the non-infected controls.

not yet possible to investigate. What our study does indicate is that in the short term the pandemic does not seem to have caused an increase in epilepsy diagnoses on a population-wide scale in Sweden.

Declaration of Competing Interest

JZ reports honoraria from UCB and Eisai for non-branded education, and as employee of Sahlgrenska university hospital (no personal compensation) being investigator in clinical trials sponsored by UCB, SK-life science, GW Pharma, and Bial.

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