New Risk Factors in Poststroke Epilepsy

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Abstract

The overall aim of the present research was to identify new risk factors for poststroke epilepsy (PSE). Specifically, we wanted to assess the impact of having a first-degree relative with epilepsy on PSE risk (Paper I), and to investigate if endovascular treatment (EVT) affects PSE risk and possible factors that modify PSE risk in EVT (Paper II and IV). Additionally, we explored if blood-brain injury markers can assess stroke severity and assist in predicting PSE or in identifying individuals of high risk of epilepsy (Paper II and III).

Family history influences the risk of epilepsy in young persons, but such association in adults is less clear. Investigations of how family history impacts PSE risk in adults are rare. We conducted a nationwide register study to estimate the effect of having a first-degree relative with epilepsy on PSE risk. We found that family history increased the PSE risk both in the univariate analysis and after adjustment for stroke severity.

EVT is a new treatment, and the literature on the risk of subsequent PSE is conflicting. EVT is indicated in large vessel occlusion, in itself, a substantial risk factor for PSE. We first assessed PSE risk after EVT in a local cohort at the Sahlgrenska University Hospital. The included individuals had severe stroke, but despite this, the incidence of PSE after EVT was only 4.4%. Blood concentrations of biochemical brain injury markers were generally higher in individuals with PSE, but the low number of individuals prevented further analysis.

Thereafter, PSE risk after EVT was assessed in a nationwide register study comparing EVT to cases receiving other acute stroke treatments matched for pre-treatment stroke severity. The incidence of PSE was lower after EVT compared to treatment with intravenous thrombolysis (IVT) or no acute treatment. EVT was associated with a lower risk of PSE in univariate analysis and after adjustment for stroke severity. Stroke severity was a risk factor for PSE after EVT. IVT in combination with EVT and no radiological infarction on day one was associated with a decreased PSE risk.

To elaborate on the biochemical results from Paper II, we conducted an exploratory local cohort study of individuals with first-ever seizures. The PSE group had increased Neurofilament light (NfL) compared to individuals with single seizures and no previous stroke.

In summary, having a positive family history increased the risk of PSE, and EVT was associated with a decreased PSE risk in cases of severe stroke. Whether biochemical brain injury markers can aid in predicting and diagnosing PSE requires further study.

Keywords: Poststroke epilepsy, Epilepsy, Seizures, Stroke, Endovascular treatment, Biomarkers

Sammanfattning

Stroke är den vanligaste identifierbara orsaken till epilepsi i Sverige. Risken för epilepsi ökar vid stor stroke, blödning, stroke innefattande hjärnbarken, och anfall i nära tid till stroke. Men långt från alla som har de riskfaktorerna utvecklar poststroke epilepsi (PSE) och de bakomliggande mekanismerna är inte fullt kartlagda. Genom att identifiera fler riskfaktorer kan personer med hög risk enklare urskiljas. Personer med hög risk kan vara aktuella för mer aktiv uppföljning så att epilepsi kan uppmärksammas och behandlas. Bättre identifiering av högriskpersoner möjliggör även urval till framtida studier som kan undersöka förebyggande behandling. Syftet med denna avhandling var att identifiera fler riskfaktorer, samt att undersöka risken för PSE hos personer som behandlas med en relativt ny strokebehandling. I avhandlingen undersöks även om hjärnskademarkörer i blod som avspeglar svårighetsgrad av stroke biokemiskt kan bidra till att förutsäga PSE.

Först undersöktes om risken för PSE ökar om en person med stroke har en förstagradssläkting med epilepsi. Det är känt att ärftlighet spelar in vid medfödd epilepsi, men ett sådant samband har inte tidigare visats hos äldre personer med PSE. Vi fann att risken för PSE är högre hos dem med en förstagradssläkting med epilepsi. Att familjehistoria har betydelse är även av vikt för att bättre förstå hur PSE uppstår.

Sedan undersöktes om endovaskulär behandling (trombektomi) vid akut stroke påverkar risken för PSE. Detta är en ny behandlingsmetod som utförs vid allvarlig akut ischemisk stroke för att återställa blodflödet. Genom att ocklusionen som hindrar blodflödet avlägsnas, kan blodflödet till hjärnan återställas. Ofta resulterar det i minskad hjärnskada och förbättrad funktion efter stroke. Långtidsrisker är ännu inte fullt kartlagda och risken för PSE efter endovaskulär behandling är inte känd.

Inledningsvis undersöktes förekomsten av PSE hos personer som genomgått endovaskulär behandling vid Sahlgrenska Universitetssjukhuset under en viss tidsperiod. Trots omfattande stroke, och av den anledningen hög risk för PSE, var förekomsten av PSE låg (4.4%). I samma studie undersöktes om

hjärnskademarkörer kunde användas för att bedöma strokens allvarlighetsgrad. Vi fann att nivåerna av hjärnskademarkörerna var generellt högre hos de med PSE, men antalet patienter var för få för ytterligare statistisk analys.

För att vidare undersöka förekomsten av PSE efter endovaskulär behandling i ett större material genomfördes en uppföljande registerstudie. Här fann vi att endovaskulär behandling var förknippat med en lägre risk för PSE jämfört med kontrollgruppen med lika allvarlig stroke som inte fick behandling. Strokens allvarlighetsgrad var en viktig riskfaktor för PSE även efter EVT.

Slutligen undersöktes om nivåer av hjärnskademarkörer i blod kunde urskilja personer med nydiagnostiserad epilepsi eller PSE. Personer med PSE hade högre nivåer av hjärnskademarkören Neurofilament light (NfL) än kontrollgruppen med ett enda epileptiskt anfall utan tidigare stroke.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Eriksson H**, Wirdefeldt K, Åsberg S, Zelano J. Family history increases the risk of late seizures after stroke. *Neurology*. Nov 2019, 93:(21) e1964-e1970. PMID:31645466 DOI: 10.1212/WNL.0000000000008522

II. **Eriksson H**, Löwhagen Hendén P, Rentzos A, Pujol-Calderón F, Karlsson J-E, Höglund K, Blennow K, Zetterberg H, Rosengren L, Zelano J. Acute symptomatic seizures and epilepsy after mechanical thrombectomy. *Epilepsy Behav.* 2020 Mar;104(PtB):106520. PMID:31526644 DOI: 10.1016/j.yebeh.2019.106520

III. **Eriksson H**, Kumar Banote R, Larsson D, Blennow K, Zetterberg H, Zelano J. Brain injury markers in new-onset seizures in adults: A pilot study. *Seizure.* 2021 Nov;92:62-67. PMID:34455195 DOI: 10.1016/j.seizure.2021.08.012

IV. **Eriksson H**, Nordanstig A, Rentzos A, Zelano J, Redfors P. The risk of poststroke epilepsy after endovascular treatment: a national cohort study. *Manuscript 2022*

Content

Abbreviations

AIS	Acute ischemic stroke
ASM	Antiseizure medication
ASS	Acute symptomatic seizures
ATC	The Anatomical Therapeutic Chemical
BBB	Blood-Brain Barrier
CD40	Cluster of Differentiation 40
CDR	The Cause of Death Register
CNS	Central nervous system
CSF	Cerebrospinal fluid
CVT	Central venous thrombosis
ECLIA	ElectroChemiLuminescence Immunoassay
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
EVAS	The Swedish National Quality Register for individuals that underwent EVT for stroke
EVT	Endovascular treatment
ICD	The International Classification of Diseases

ICH	Intracerebral hemorrhage
ILAE	International League Against Epilepsy
IVT	Intravenous thrombolysis
GFAP	Glial fibrillary acidic protein
MCA	Middle cerebral artery
MGR	The Swedish Multi-Generation Register
mRS	modified Rankin Scale
NIHSS	The National Institutes of Health Stroke Scale
NfL	Neurofilament light
NPR	National Patient Register
NSE	Neuron-specific enolase
PSE	Poststroke epilepsy
S100B	S100 calcium-binding protein
Simoa	Single-molecule array
Tau	microtubule-associated protein tau
TRPM6	Transient receptor potential cation channel subfamily M member 6
4HNE	4-hydroxy-2-nonenal

Definitions in short

Stroke	A stroke is an acute medical condition that occurs when the blood supply to the brain is interrupted and with symptoms lasting longer than 24 hours.
Epilepsy	Epilepsy is defined as a recurring predisposition to generate epileptic seizures.
Seizure	A seizure is the occurrence of signs or symptoms caused by excessively synchronously activated neurons.
Poststroke epilepsy	One or more seizures that occur >7 days after stroke count as poststroke epilepsy.
Acute symptomatic seizures	Acute symptomatic seizures are seizures that occur within the first week after stroke.

Introduction

This thesis explores new risk factors for poststroke epilepsy (PSE) to improve PSE prediction. Identifying additional risk factors could aid in finding high-risk individuals to have optimized follow-up regimes to detect and treat seizures after stroke. Such knowledge would also facilitate studies of preventive treatment.

Stroke is the most common identifiable cause of epilepsy after middle age (1, 2). One single seizure >7 days after stroke qualifies for a diagnosis of poststroke epilepsy because of the high risk of recurrence (3). The incidence of PSE is around 6.7-7.9% after ischemic stroke (4, 5) but has been reported to be up to 15% (6, 7) in younger individuals and around 9.2-12.4% after hemorrhagic stroke (8, 9). With an aging population, the incidence of PSE will most likely increase.

There are well-established PSE risk factors; cortical lesion (10, 11), large stroke (12, 13), hemorrhagic stroke (8), young age (14), and acute symptomatic seizures. Tools have been developed to calculate the risk of PSE based on combinations of these risk factors (9, 12, 15). However, not all individuals with such stroke characteristics develop PSE, and the pathogenesis is not well understood.

The risk of PSE after the latest development in stroke revascularization therapy with EVT has not been fully explored. EVT has revolutionized the treatment of stroke caused by large vessel occlusions (16, 17), and because a growing number of individuals are being subjected to this treatment (18), long-term risks of PSE are important to determine.

This thesis presents a compilation of studies on new risk factors of PSE. Respectively, these studies describe the impact of having a first-degree relative with epilepsy on PSE, PSE risk depending on acute stroke treatment, and the utility of brain injury markers to biochemically reflect stroke severity and predict PSE.

Knowledge gaps and objectives

Table 1. EVT = endovascular treatment; PSE = poststroke epilepsy.

Paper	Knowledge Gaps	Objectives
I	Evidence supports an influence of hereditary factors in other forms of acquired epilepsy, and genetic alterations have been associated with an increased PSE risk. However, a hereditary influence on PSE risk from existing cohort studies is uncertain, most likely because adequately powered studies are rare.	To evaluate the impact of having a first-degree relative with epilepsy on PSE risk.
II	There are uncertainties about the effect of endovascular treatment on PSE risk. Evidence mainly exists of the risk of seizures within the first week of stroke.	To assess the incidence of PSE after endovascular treatment and explore if brain injury markers could predict PSE.
III	Blood-brain injury biomarkers are increasingly used in the clinical setting to assess neurological damage, but to date, no brain injury marker has been identified to predict PSE or epilepsy.	To investigate the association of brain injury markers with seizures and epilepsy in individuals with new-onset seizures.
IV	The results from Paper II suggested that the PSE risk was low after EVT in large vessel occlusions, but due to the small sample, a more extensive study is warranted for increased generalizability.	To investigate PSE risk after endovascular treatment and possible factors that modify the risk.

Background

Pathophysiology

Seizures after stroke are classified into acute symptomatic seizures (ASS) or PSE. ASS occurs within a week after a stroke and is caused by reversible metabolic disturbances and is not sufficient for a diagnosis of epilepsy (19). In contrast, PSE is defined as a seizure that occurs seven days or more from a stroke (20). The exact underlying mechanisms of PSE are not completely understood. Supposedly, the brain changes during the latent period between stroke and PSE and becomes more prone to generate seizures. This process is called epileptogenesis. The onset of PSE is typically within a year after stroke (21, 22), although the risk stays elevated for many years (23, 24).

One mechanism believed to be involved in PSE pathogenesis is gliotic scarring (25, 26). Gliosis occurs when astrocytic cells become activated in response to acute injury (27). Presumably, the gliotic scar provokes seizures from the surrounding viable but damaged perilesional tissue. Inflammation is another frequently discussed mechanism (28), but the exact contribution is unclear. Human drug-resistant epilepsy specimens show a reduced anti-inflammatory response (29). Possibly, PSE could be caused by an insufficient inflammatory response that could restrain the healing of damaged neurons after stroke. Animal models have also found that inflammation may disrupt the electrophysiological homeostasis due to activated immune microglial cells, which would alter the seizure threshold (30).

PSE epileptogenesis also involves processes localized distant from the stroke lesion (31). Animal models of PSE have found widespread astroglial changes in both the cortex and hippocampus (32) and sprouting of mossy fibers both ipsilateral and contralateral to the stroke lesion (33). Studies on functional brain networks in focal epilepsy demonstrate changes in connectivity patterns over different brain regions (34, 35), further illustrating the complexity of PSE pathogenesis.

Findings from animal studies cannot be directly translated into an understanding of human epileptogenesis, given that rodents and human brains

have different anatomical and functional qualities. Because of the long latency of PSE, performing large-scale animal experiments requires extended care of animals and technical surveillance to detect seizures. For this reason, studying PSE pathogenesis is difficult (33, 36) why exploring new risk factors in clinical research can add to the understanding.

Genetic predisposition

Genetics are important for the development of epilepsy in children and the young (37-40). In adults, the impact of a genetic vulnerability is less evident. After a stroke, a positive family history increases the risk of an acute symptomatic seizure (41), but adequately powered clinical studies on PSE are rare.

Most clinical studies on the impact of family history are either local (42) or obtain epilepsy diagnoses in relatives by questionnaires answered by the proband instead of direct screening of the relative´s medical charts (10, 43). This may lead to many missing epilepsy diagnoses. The rate of reported epilepsy diagnoses captured by interviewing probands compared to diagnoses identified in medical charts of relatives is only 50-62 % (44). Identifying family history can be challenging, which was also indicated in a study by Beghi et al., who reported a positive family history only in 1.7% (45).

A Danish study investigated the impact of family history on epilepsy risk after traumatic brain injury. Depending on the statistical method, the results showed an inconsistent impact of family history on epilepsy risk (46). Nevertheless, the findings raise the question of whether family history influences risks in other types of acquired epilepsy. In one study of acquired focal epilepsy of mixed etiology, family impact did not increase the risk in young (38) but likely did not capture many PSE cases. Other experts have argued for a genetic contribution to focal epilepsy, partly because of the associations with specific genes (39).

There is evidence that individuals with specific gene alterations carry a greater risk of PSE. Compared to stroke controls, individuals with PSE more often carry the alleles rs671 (47), T allele (48), and the TRPM6 rs2274924 C allele (49). These gene variations have been associated with oxidative stress, inflammation, endothelial integrity, and cellular electrophysiology. The presence of polymorphism in PSE cases and the findings of family impact in acute symptomatic seizures suggest that some hereditary factors might influence PSE risk. Therefore, we set out to determine the impact of family history on PSE risk in a large nationwide study with a robust assessment of family history from register data in Paper I.

Risk factors

Epidemiological data have identified several stroke characteristics and clinical characteristics that increase PSE risk. Many of the studies have considerable follow-up time, which allows identification of seizures long after the index stroke. Consequently, this enabled investigations of significant risk factors for PSE.

Stroke severity

A major risk factor of PSE is stroke severity, demonstrated in prospective population-based studies, multicenter studies (10, 50, 51), and several smaller studies (41, 43, 52). Clinical deficit or disability can be assessed with several scores. The National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) are the most frequently used. NIHSS ranges from 0 – 42, and mRS from 0 – 6. Higher values represent more severe stroke. Typically, NIHSS is used in the acute stroke phase, and mRS at 30 or 90 days after stroke to assess outcome (53). Both scales are used in the clinic and in research to estimate neurological deficits. There are additional scales to assess stroke severity, for example, the Glasgow coma scale, the Scandinavian Stroke Scale, and the Canadian Neurological scale (54).

Localization of stroke

Another major risk factor is cortical stroke (11, 41, 55). Cortical stroke increased PSE risk by four times in one meta-analysis (56) and 11 times in a large retrospective study from China (43). The risk of PSE in ischemic stroke is also influenced by which circulatory territory is affected. Anterior circulation stroke carries a higher PSE risk than posterior stroke (11, 57). In superior sagittal sinus thrombosis, the risk of acute symptomatic seizures (58) and PSE (59) is also elevated, and seizures are common after cerebral venous thrombosis (CVT) (60).

Stroke type

Primary intracerebral hemorrhage (ICH) constitutes a higher risk of PSE development. The risk is more than twofold compared to ischemic stroke (21, 56, 61). Hemorrhagic stroke is a risk factor for PSE also in young individuals (57), with an absolute risk as high as 31% in adults under the age of 50 (21). Hemorrhagic transformation (HT) of ischemic stroke, either spontaneously or after acute stroke treatment, increased PSE risk by five times in one study (62).

Age

Young age is also a risk factor for PSE (11, 55). Examples include an extensive study of young individuals with ischemic stroke, in which the incidence of PSE (16%) was considerably higher than the risk after ischemic stroke in general (21).

Sex

The influence of sex on PSE risk is less clear. Several robust studies, including meta-analyses, indicate that sex does not affect the risk of PSE (11, 14, 56, 61), so occasional studies finding that male sex increases PSE risk may reflect accidental associations (57).

Acute symptomatic seizures

Another predictor of PSE risk is acute symptomatic seizures (14, 57). Acute symptomatic seizures are associated with an almost fourfold increased PSE risk (56).

The risk of PSE depending on stroke treatment

Stroke affects approximately 20 000 individuals in Sweden each year (63). Most strokes are caused by an occlusion of a cerebral artery (ischemic stroke approx. 85%). Stroke can also occur if a cerebral blood vessel wall ruptures (hemorrhagic stroke approx. 15%). This thesis focus on PSE-associated risks of treatment of ischemic stroke, the most common stroke type.

Treatment of acute ischemic stroke is by intravenous thrombolysis (IVT) alone or in combination with endovascular treatment (EVT) when no contraindications exist. The therapies aim to dissolve or remove the ischemic thrombus and restore the blood flow to the affected area to minimize the injury. Both IVT and EVT improve independence after stroke (16, 64, 65). The stroke treatments have a narrow time window in which they may be given, IVT is initiated within 4.5 hours from stroke onset, and EVT can be performed up to 24 hours after onset of symptoms in selected cases. Compared to IVT, EVT has shown superiority with better functional outcome in large vessel occlusion (16, 17). Since EVT is a relatively new treatment, long-term risks are not well-characterized.

The occurrence of seizures after EVT has mainly been studied with regard to acute symptomatic seizures. The ASS incidence is similar after EVT (ranging between 2.4 - 3.8 % (66-69) compared to the general incidences of ASS in ischemic stroke, ranging from 1.6 to 5.5% (70-72). The occurrence of ASS after IVT alone, in addition to EVT, or after EVT only is low (3.8%) (73). EVT is not associated with ASS when studying EVT alone (74) or in combination with IVT (69).

There is still uncertainty about whether EVT has an effect on PSE occurrence. The prevalence of both early and late seizures combined has been reported at 6.7% (75), or 12.9% after stroke treatments, including EVT (76). The composite outcome and grouping of different treatment modalities limit understanding of PSE risk specifically, so the long-term risks remain undetermined. One study found no significant difference in PSE risk between EVT compared to no reperfusion treatment (77). We set out to investigate the occurrence of PSE after EVT and associated risk factors in Paper II and IV.

Brain injury markers

There have been significant advances in neurology in using biochemical brain injury markers to quantify brain injury and predict disease. Brain injury markers are commonly used in neurointensive care to assess neurological damage. For instance, the use of Neuron-specific enolase (NSE) in prognostication in ischemic brain injury and after cardiac arrest (78) and the use of S100 calcium-binding protein (S100B) to predict outcomes after head trauma (79). Cerebrospinal fluid (CSF) microtubule-associated protein tau (tau) is used in diagnosing Alzheimer's disease (80), and plasma tau seems promising in distinguishing Alzheimer's disease from controls (81). Levels of plasma Neurofilament light (NfL) correlate with CSF levels in Alzheimer's disease (82), suggesting that brain injury markers obtained from blood reflect processes in the brain. Because of the invasiveness of CSF samples, there is increasing interest in using blood-based brain injury markers to estimate brain injury severity.

The concentrations of brain injury markers rise after stroke and reflect different cellular injury or activation aspects. In this thesis, we investigate if brain injury markers can be used to assess stroke severity or predict PSE. We specifically examine five brain injury markers in current clinical use; NfL, NSE, tau, S100B, and Glial fibrillary acidic protein (GFAP). NfL is a part of the axonal cytoskeleton in a neuron and a marker of subcortical damage (83). (84). Tau is a protein that stabilizes the neuronal microtubules and is a marker of axonal damage (83). NSE concentrations correlate with neuronal cell death and increase after acute injury (85). GFAP and S100B are markers of astroglial cell injury, where S100B is a cytokine produced by astrocytes and GFAP is a marker of astrogliosis (86) and inflammation in epilepsy (29). S100B increases shortly after stroke (<7d) and correlates with stroke severity. The concentrations decline at around three weeks after a stroke (87) and are almost at baseline at three months, and no longer correlate with neurological damage (88). NSE and GFAP are neuron-specific (85), while S100B, to some part, is expressed in the periphery in adipocytes, melanocytes, and chondrocytes (89). NfL is also neuron-specific but not limited to neurons in the central nervous system (CNS) (83, 90).

Some studies have investigated brain injury markers in seizures and epilepsy. Concentrations of CSF GFAP increase in children after seizures (91), and

CSF tau increases in adults with refractory status epilepticus (92). Individuals with focal onset drug-resistant epilepsy have increased blood NfL (93). When S100B was investigated within 6 hours after stroke, PSE cases had decreased levels of blood S100B compared to controls (94). Contrary, a smaller cohort study found increased concentrations of blood S100B in individuals with temporal lobe epilepsy (95). The present data suggest a correlation between concentrations of different brain injury markers with epilepsy, but if brain injury markers can predict seizures is still uncertain.

Measurement of blood-brain injury markers would be a compelling way to move closer to a noninvasive individual PSE risk assessment. Potentially, brain injury markers could also assess the degree of brain injury and give new insight into the epileptogenic process.

Methodological considerations

This thesis investigates new risk factors of PSE, EVT-associated risks, and the potential to use brain injury markers in predicting seizures by different methodological approaches. Two of the studies were retrospective and register-based, allowing nationwide investigations (Paper I and IV), and two were cohort studies at the Sahlgrenska University Hospital. One cohort study on brain injury markers had prospectively included individuals but was retrospective in the study of the PSE diagnosis (Paper II). The other included cases prospectively (Paper III).

Table 2. Overview of included Papers in the thesis

	Paper I Family impact on PSE risk	Paper II ASS and PSE after EVT	Paper III Brain injury markers in new-onset seizures	Paper IV PSE after EVT
Study design	Register study	Cohort study	Cohort study	Register study
Size	86,550	90	62	5,200
Study period	2001 – 2012	2013 – 2016	2016- 2019	2015 – 2019
Inclusion criteria	All stroke individuals > 18 years of age in Riksstroke born after 1932	Acute anterior ischemic stroke that underwent EVT	Unprovoked new-onset seizure at age > 25 years	All EVT cases 18-99 years of age
Exclusion criteria	Prior seizure-related diagnosis.			
	No identifiable relative	EVT contra-indications	Brain tumor	Brain tumor

Abbreviations: ASS = Acute symptomatic seizures; EVT = endovascular treatment; PSE = poststroke epilepsy.

Registers

Sweden has several population-based registers that hold large sets of individual data and variables. National Health Data Registers are administered by the government, while quality registers are initiated and maintained by health care professionals to improve the quality of care. Since all Swedish inhabitants have a unique personal identity number, data from different registers can be linked, enabling research on many variables and their association.

Data collection

In Paper I and IV, several Swedish registers were combined to 1) assess the impact on PSE risk when having a positive family history of epilepsy, 2) analyze the risk of PSE after endovascular treatment. Brain injury markers were obtained and analyzed locally at the Sahlgrenska University Hospital (Paper II and III). The National Board of Health and Welfare anonymized the register data before delivery.

National Registers held by The National Board of Health and Welfare

National Health Data Registers are maintained by the National Board of Health and Welfare and are funded by the government. The registers can be used for quality assurance, evaluation, statistics, follow-up, and research. The registers hold data of all cases in a population, such as hospital visits or outpatient visits, prescribed drugs, and death dates. Reporting by caregivers is mandatory, and no data may be deleted. In this thesis, data was collected from the Swedish National Patient Register (NPR), the Medical Prescribed Drug Register (MPDR), the Cause of Death Register (CDR), and the Swedish Multi-generation Register (MGR).

The National Patient Register

Epilepsy-related diagnoses were collected from the NPR based on diagnostic codes from the International Classification of Diseases, ICD-9th/10th revision. The register was established in 1962 for psychiatric diseases, and later, registration of inpatient care (somatic, geriatric, and psychiatric) was included and reporting became mandatory. Reporting became nationwide in 1987. In 2001, the NPR also included specialized outpatient care with a coverage of 97 % (96), somewhat lower than the coverage for inpatient care (99%) (97). Validation studies on stroke diagnoses show that a diagnosis of stroke is accurate in 89% (98). An epilepsy diagnosis (G40) has a positive predictive value of approximately 90%, in which a diagnosis is accurate when compared to medical charts (99). Primary care diagnoses are not registered in the NPR.

The Cause of Death Register

The Cause of Death Register contains data on deaths and underlying causes from 1961 on all Swedish residents. It is updated once per year (100). Only 0.9% of deaths had missing data on the underlying cause in 2015 (101).

The Prescribed Drug Register

The Prescribed Drug Register has had complete registration of drugs dispensed at pharmacies since 2005. The register does not state indications of prescriptions and does not include medications dispensed at hospitals. Registrations are monthly with complete coverage (102). The Anatomical Therapeutic Chemical (ATC) codes are used for categorization.

The Swedish Multi-Generation Register

The Swedish Multi-generation register holds information on index persons' mothers and fathers and indirectly siblings if born after 1932 and registered in Sweden after 1961. The register contains data on emigration and adoption and is updated annually (103).

National Quality Registers

The Swedish Stroke Register

Quality registers are used to improve care and research, and reporting is optional by both the units and the individuals with the specific condition. In this thesis, individuals with stroke were identified from the Swedish Stroke Register (Riksstroke). The register holds data on given stroke care; acute management, comorbidities, follow-up data, etc. Variables on stroke severity were assessed from Riksstroke. The Swedish Stroke Register was established in 1994, and all Swedish Hospitals which execute acute stroke care report to the registry. The coverage exceeds 90% after 1998 (63), and a stroke diagnosis is accurate in 95% of cases (104).

The EVAS register

This thesis also used the Swedish National Quality Register for individuals that underwent EVT for stroke (EVAS register) to assess PSE risk after different acute stroke treatments. The EVAS register includes all individuals treated with EVT, and in 2020, the coverage was high (97 %) (18). A validation investigation by the National Board of Health and Welfare demonstrated a coverage of 96% compared to reported data in the NPR in 2019 (105).

Variables

Stroke severity was assessed with The National Institutes of Health Stroke Scale (NIHSS). There is missing data on NIHSS in Riksstroke. NIHSS was introduced toward the end of data acquisition in Paper I. Therefore, dependence (by function in mobility and independence) at the three-month follow-up was used as a proxy for stroke severity in the survival-adjusted analyses.

Validation of registers

The incidence of PSE in previous Swedish epidemiological studies is well aligned with incidences from other epidemiological reports, which advocate that Swedish registers are robust and may be used to investigate PSE incidences and risk factors (8). Using administrative data is advised to be an appropriate way to identify epilepsy diagnoses in epidemiological research, and robustness increases further when combining diagnostic codes with antiseizure medication (ASM) (106). Therefore, in one sensitivity analysis in paper IV, we defined an event (outcome) as a seizure-related diagnosis and a prescription of an ASM.

Quantification of brain injury markers

Brain injury markers are breakdown products from neurons and astrocytes. In Paper II and III, the immunoassays ECLIA (ElectroChemiLuminescence Immunoassay) and Simoa (Single-molecule array) were used to measure the levels of the brain injury markers GFAP, NSE, tau, S100B, and NfL in plasma or blood in individuals with seizures. Immunoassays measure the substrate levels using antibodies.

ECLIA has high sensitivity and selectivity. The technique involves a plate with a capture antibody, onto which the sample and two labeled detection antibodies are added. A sandwich complex is formed with the antigen. Microbeads are added, and an immunocomplex is formed. This can be quantified by a light signal from paramagnetic beads and reactions after the addition of specific substrates and voltage. The signal is equivalent to the concentration of the sample.

Simoa is a new automated technique with increased sensitivity that isolate individual immunocomplexes on paramagnetic beads with standard ELISA (Enzyme-linked immunosorbent assay) reactants. In Simoa, paramagnetic particles are bound to target-specific antibodies. Detection antibodies are added, and immunocomplexes are formed. The plate consists of 200 000 wells onto which one immunocomplex can be held.

Statistics

Paper I and IV analyzed the data by Kaplan-Meier and Cox Regression (Paper I and IV). The primary outcome variable (event) - PSE - was defined as a seizure-related diagnosis (ICD-10 codes G40 [epilepsy], G41 [status epilepticus], and R56.8 [seizures]) registered at least seven days after the stroke to avoid inclusion of acute symptomatic seizures.

Survival-adjusted analyses allow estimation of incidences and risks over time and take into account cases lost due to death or when an event has occurred. This improves the estimate of the impact of the studied factor (in this case, the impact of family history or EVT treatment). Cox regression analysis not only takes into account the remaining cases in the analysis but also allows for the adjustment of confounding factors.

In Paper IV, we controlled for confounding first by matching of groups. After applying the exclusion criteria, the groups were not equal with regard to matching variables, so a correction of confounding was also made. In Paper IV, the covariates reaching significance in univariable analysis were excluded in a backward-stepwise approach to identify final Cox proportional hazard multivariable models. In this way, relevant PSE covariates were simultaneously evaluated and weighed. Simultaneously, associated risk factors that increase PSE risk after EVT could be assessed, and confounders could be controlled.

No imputations were made in cases with missing covariate data. Instead, we calculated post-treatment NIHSS scores from available NIHSS data (NIHSS is reported at different time points following stroke) in Paper IV. And in both Paper I and IV, several models were tested with different stratifications for stroke severity, not to introduce any bias or incorrect estimates.

Group comparisons in Paper II and III were made with independent sample t-test, unpaired two-sample t-test, and Kruskal-Wallis test with Benjamini-Hochberg adjustments for multiple comparisons. All tests were 2-sided, and the significance was defined as $p>0.05$.

Data were analyzed using IBM SPSS Statistics for Windows and Mac, version 25 and 26 (IBM Corp., Armonk, N.Y., USA), and Graph Pad Prism®

version 9.0.1 for Windows (GraphPad Software, San Diego, California USA, www.graphpad.com).

Ethical considerations

All projects obtained ethical approval from the regional ethics committees of Gothenburg and Uppsala (805-17, 013-13, 061-76, 844-15). In Paper II and III, informed consent was given before collecting blood samples.

All hospitals and outpatient centers report to National Health data Registers. Research on Swedish registers is approved by the relevant ethical bodies (former regional ethics committees, now the Ethics Review Authority), which can waive the need for individual informed consent, as was the case for the register studies in this thesis. Data obtained from registers present no personal data. The data was anonymized by Statistics Sweden before being given to the authors and handled with absolute confidentiality.

Results

A family history of epilepsy increases PSE risk

Paper I was a nationwide register-based study that investigated the impact of having a first-degree relative with epilepsy on PSE risk (107). The study included 86,550 adult stroke cases with no prior seizure-related diagnoses. The median age was 65 years (range 19-79). There were 14.4% with intracerebral hemorrhage and 85.6% with ischemic stroke. A diagnosis of epilepsy in relatives was ascertained in 8.6%. The total PSE incidence was 8.4% (n=7,307). In survival-adjusted analyses, the risk of PSE was higher in individuals with a family history compared to those not having a family history of epilepsy both at two years: 6.8% (95% confidence interval [CI]: 6.2-7.4) versus 5.9% (95% CI: 5.7-6.1), and at five years: 9.5% (95% CI: 8.7-10.3) versus 8.2% (95% CI: 8.0-8.4) (fig 1).

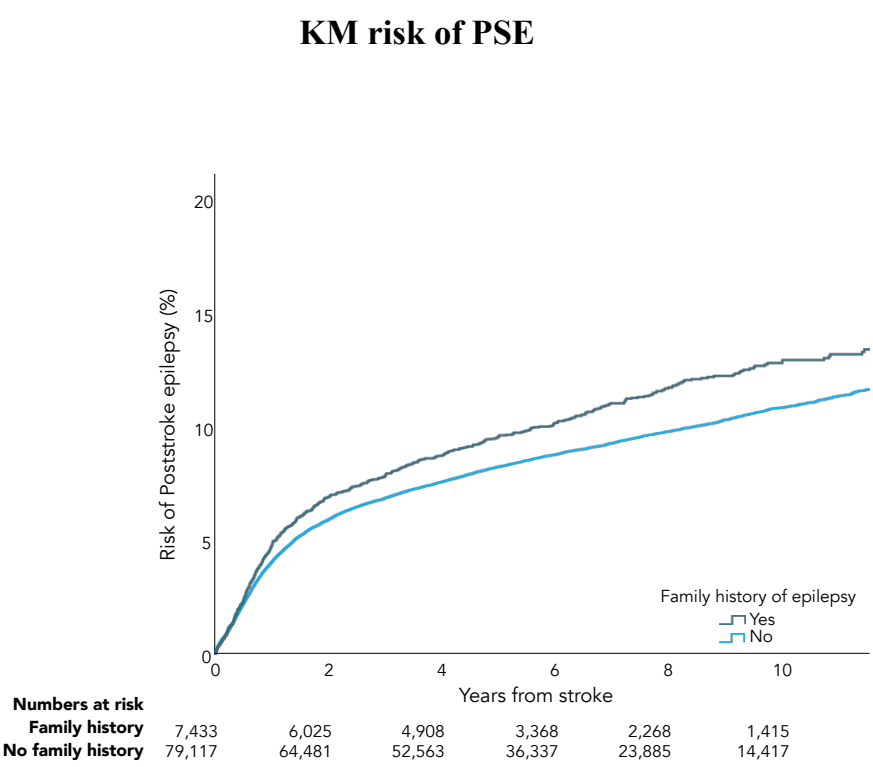

Figure 1. Kaplan-Meier curve on PSE risk with or without a family history of epilepsy. This figure is a modification of a figure from the article "Family history increases the risk of late seizures after stroke." Neurology Nov 2019, 93:(21) e1964-e1970.

The univariate Hazard ratio (HR) for PSE in the presence of a positive family history was 1.17 (95% CI: 1.08-1.26). Family history increased the risk of PSE after adjustment for age, sex, stroke type, number of relatives, living conditions, and mobility after three months, HR 1.16 (95% CI: 1.06–1.26). When NIHSS was used to stratify for stroke severity, the impact was insignificant because of the low number of cases with available NIHSS data from Riksstroke. In the model adjusting for stroke severity by mobility at three months, the impact of family history was greater in individuals with a less severe stroke, implying that stroke severity is a stronger determinant of PSE than family history.

All sensitivity analyses showed similar results to the primary analyses. The results did not seem to be influenced by a higher familial risk of stroke. The HR correcting for stroke before epilepsy in relatives was 1.18 (95% CI: 1.09–1.28) and 1.20 (95% CI: 1.10-1.30) after excluding relatives with stroke at any time point.

To avoid the inclusion of provoked seizures, sensitivity analyses excluding cases where the use of proconvulsant medications was also done with similar results as the main analysis. When the event was defined as the specific epilepsy diagnosis (ICD-10 code G40), instead of any seizure-related code, the results were largely unchanged HR 1.15 (95% CI: 1.05-1.25).

PSE after Endovascular Treatment

Paper II

The incidence of PSE after EVT was investigated in individuals included in the AnStroke trial, a randomized controlled trial that compared general versus conscious sedation during EVT at the Sahlgrenska University Hospital (108). The AnStroke trial also collected blood-brain injury markers.

A total of 90 individuals were included. The median age was 72 years (range 65-80), and 46% were females (109). The median admission NIHSS was 18 (range 15 – 22). Successful recanalization was achieved in 90% and the median discharge NIHSS was 2 (range 0 – 10). Only four individuals developed PSE (4.4%). The results indicated that the PSE group had higher concentrations of the brain injury markers at some time points from stroke to the follow-up at three months, and the levels were generally above the cohort median. Because of the low incidence of PSE, further statistical analysis of the brain injury marker levels was not possible.

Paper IV

Subsequently, we performed a nationwide register study on PSE risk after EVT. The study included all EVT procedures in Sweden between 2015 and 2019 (Paper IV). Two control groups with IVT treatment or no acute treatment matched by age, sex, and stroke severity were identified. The total cohort included 5,200 stroke cases.

The median age was 73 years (IQR 16). The median admission NIHSS was 13 (IQR 10), and the median post-treatment NIHSS was 7 (IQR 12). The overall incidence of PSE was 7.9%. The lowest PSE incidence was seen after EVT, followed by IVT, compared to no acute treatment.

After two years, the risk of PSE was almost doubled after no treatment compared to treatment with EVT and slightly higher than after IVT (fig 2).

When comparing the three treatment groups in survival-adjusted analysis, the risk of PSE was lower after EVT compared to no acute treatment. The PSE incidence after EVT remained lower after correction for stroke severity by post-treatment NIHSS and mobility at three months. When comparing the risk of PSE in the IVT group compared to no acute treatment, the results were insignificant both in the crude model and in two models adjusting for stroke severity by post-treatment NIHSS and living and mobility at three months.

In the first sensitivity analysis, the event was defined if cases had both an epilepsy-related diagnosis and a prescription of antiseizure medication. In this analysis, the PSE risk was comparable to that of the main analysis both in the univariate model and after adjustment for age and stroke severity by mobility at three months.

When epilepsy was defined by the ICD-10 code G40 (epilepsy) instead of any seizure-related code, the results were largely unchanged both in the univariate model and after correction for stroke severity by mobility at three months.

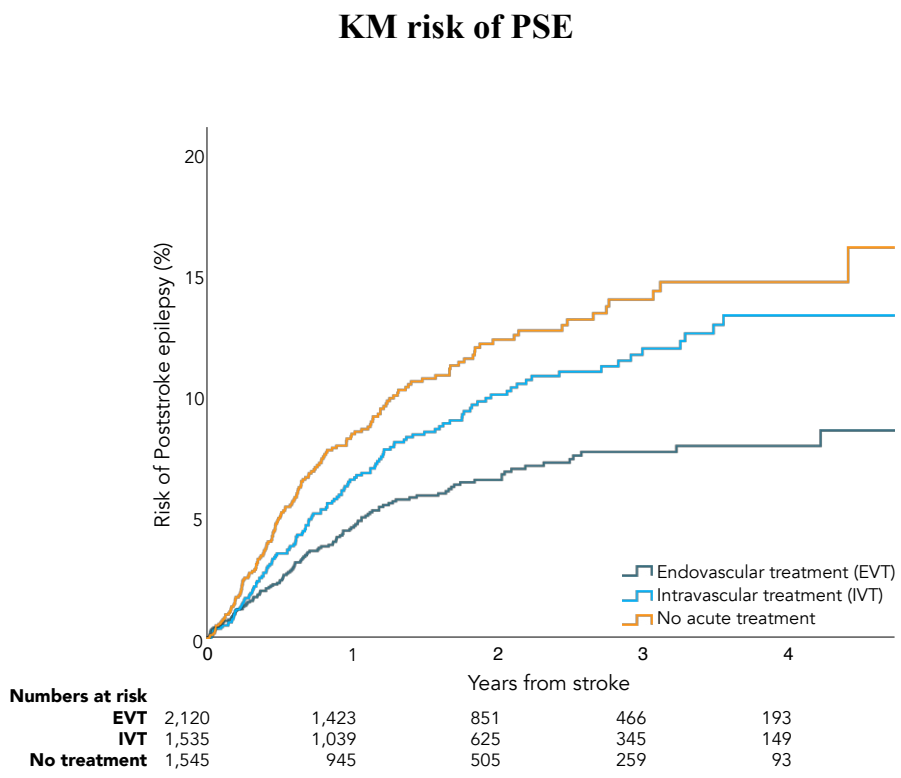

Figure 2. Cumulative risks after endovascular treatment (EVT), intravenous treatment (IVT), or no acute treatment in acute ischemic stroke (log-rank p<0.001).

Factors that modify PSE risk in EVT

Markers of stroke severity increased the PSE risk in multivariate analyses; large stroke exceeding >33% of the middle cerebral artery´s (MCA) territory on day one after stroke, higher post-treatment NIHSS, need of assistance three months after stroke, or living in a care home (Table 3). Interestingly, we found some factors associated with a decreased risk of PSE after EVT; IVT prior to EVT, and no signs of infarction on follow-up CT on day one. Hemorrhage was only associated with PSE in EVT in the univariate analysis and not in the multivariate analysis. For more detailed descriptions of associated risks, see Paper IV.

Table 3. Factors influencing PSE risk in EVT in multivariate models. EVT = endovascular treatment; IVT = intravenous thrombolysis; PSE = poststroke epilepsy; NIHSS = the National Institutes of Health Stroke Scale; MCA middle cerebral artery.

Increased PSE risk	Decreased PSE risk
Infarction exceeding >33% of the MCA territory on day one	IVT prior EVT
Higher post-treatment NIHSS	CT with no infarction at day one
The need of assistance when living at home three months after stroke	
To live in a care home at three months after stroke	

Brain injury markers as predictors of PSE

In Paper III, we included individuals with first-ever seizures and measured concentrations of brain injury markers (110). Based on clinical data, participants were classified as having a single seizure, epilepsy, or PSE.

The median age was 53 years (IQR 21) in the single seizure group, 51 years (IQR 30) in the epilepsy group, and 72 years (IQR 23) in the PSE group. Counting from the first-ever seizure, the brain injury markers were obtained after a median of 38 days (IQR 30) in the single seizure group, after 87 days (IQR 286) in the epilepsy group, and after 43 days (IQR 64) in the PSE group.

Concentrations of GFAP and NfL increased with age ($p = < 0.0001$ and $p = 0.0014$). The absolute concentrations of S100B were increased in epilepsy and PSE compared to the single seizure group ($p = 0.0023$ and $p = 0.0162$). NfL and GFAP were increased in the PSE group as opposed to the single seizures ($p = 0.0027$ and $p= 0.0243$). There were no group differences in Tau or NSE.

After age adjustments, S100B was higher in individuals with epilepsy versus in individuals with single seizures ($p = 0.0021$). Concentrations of NfL were higher in the PSE group than in the single seizure group ($p = 0.0180$).

Table 4. Key points of the included Papers in this thesis. EVT = endovascular treatment; IVT = intravenous thrombolysis; PSE = poststroke epilepsy;

Key points
Family history increased the risk of PSE
EVT was associated with a lower risk of PSE compared to IVT or no acute treatment
IVT in addition to EVT decreased the risk of PSE

Discussion

Strengths and limitations

The strength of this thesis lies in the mixed-method approach, which allows broad investigation of new risk factors for PSE. Estimating PSE incidence and risk factors using nationwide populational data has several advantages. Register research enables comparisons between groups with different exposures, e.g., having a family member with epilepsy on PSE risk or the impact of EVT treatment on PSE risk. A large amount of data in the registers allows the computing of several sensitivity analyses. The generated risk estimates could potentially be compared to other countries with a similar healthcare system as Sweden. As opposed to the register-based method, the cohort studies with a smaller data set facilitated meticulous detection of epilepsy diagnosis and follow-up. The following chapter will discuss the main strengths and limitations of the Papers included in this thesis.

Table 5. Table of strengths and limitations of register studies

Strengths	Limitations
Data sets with high coverage	Missing covariate data
Large sample size – more precise results	Lack of variables in the registers
Low recollection bias – greater generalizability	Measurement errors
Long-term follow-up	
Minimal loss to follow-up	
Low risk of inclusion of acute symptomatic seizures	

Register-based studies

Registers hold large data sets on factors that could possibly modify the PSE risk. By linking several registers with the personal identity number, comprehensive investigations of variables and their associations are possible. Register research enables in-depth investigation of many variables, and the risk of a specific outcome can be studied over a long period. One significant advantage of register research is that data is already collected. First, it rules out recollection bias (family history or epilepsy diagnosis). Second, PSE is most common in older individuals who may be lost to follow-up (which could be a common problem in case-control studies). On the other hand, the data is limited to the content of the registers and their quality. Register data allows for imputation errors, misdiagnosis, and missing data. Moreover, the registers hold no information on seizure frequency and severity.

Paper I

While the methodology allowed investigation of the impact of family history and factors that modify PSE risk in EVT in a large sample size, limiting the possibility of data distortion and selection bias, there are also limitations with the design. The main limitation was the establishment of the NPR as late as 1987, which could lead to missed diagnoses in relatives. The NPR also has a lower coverage for foreign-born individuals. Second, the use of NIHSS to evaluate stroke severity was implemented in Swedish stroke care in 2012 (toward the end of Paper I). At that time, the reporting rate was only 47% (111). As a consequence, few cases were available in the Cox models that used admission NIHSS to stratify for stroke severity. The low number of cases is the most probable explanation for the non-significant Hazard ratios in the presence of a family member with epilepsy in this model.

Paper IV

The rate of reporting NIHSS into Riksstroke increased over the years. In 2019, the rate of NIHSS reported was 61% (112). However, in Paper IV, the control groups were matched by admission NIHSS resulting in a low number of missing NIHSS data. Some variable information on follow-up NIHSS was missing, but this was not a major issue since post-treatment NIHSS (the last available NIHSS score) and dependence at three months were used as a proxy for stroke severity.

Instead, there is a possibility for selection bias in Paper IV since EVT is only accessible at University hospitals located in larger cities. Individuals living in rural areas might not reach an EVT center within the time window in which EVT can be performed. Often, individuals living in rural areas are first assessed in a county hospital before being transported to a University hospital (when indicated). A recent study found that most (73.7%) individuals with acute ischemic stroke initially arrive at a regular stroke unit, whereas only 26.3% arrive directly at EVT the first 6 hours after onset of stroke symptoms (113).

Accuracy of epilepsy diagnosis

One major concern in register research is whether the measured outcome is accurate. Misdiagnosis of seizures or epilepsy diagnoses could potentially disturb the results. A recent Swedish study on Riksstroke found that 85% of PSE cases receive a formal epilepsy diagnosis (114), highlighting this issue. However, most PSE diagnoses (73%) were received after one unprovoked seizure, according to the latest definition from the International League Against Epilepsy (ILAE) (3). In paper I and IV, we defined PSE either as having a diagnosis of epilepsy or a single seizure after stroke to increase detection of PSE cases. The risk of misclassification between acute symptomatic seizures and PSE should be small because diagnostic codes in the NPR are linked to the admission date.

Competing risks

In the two register-based studies, we used Kaplan-Meier analyses to assess the univariate risk of PSE at different time points. Prediction is more precise the more cases that are being included, and because of this, risks can be overestimated toward the end of the study period. Further overestimation might occur because of competing risks. Kaplan-Meier is based on the assumption of independent censoring. Cases lost to follow-up because of death will be assumed to have the same risk of an event as the remaining cases. As a result, the investigated risks tend to be overestimated with time (115).

On the other hand, it is possible that detection of PSE is not complete, which would underestimate the PSE risk. Evaluation of seizures in older individuals with non-convulsant symptoms can be difficult. Moreover, older individuals that seek medical attention in primary care or live in care homes risk not being included when using Swedish registers that only collect data on diagnoses from hospitals or outpatient clinics. However, this scenario would probably be rare as seizures often lead to emergency visits where diagnostic codes are reported to the NPR.

Cohort studies

The strength of the biomarker studies is that the cohort design allows secure assessment of epilepsy diagnosis by medical chart review. Another strength of the prospective cohort study design in paper III is that we could control that included individuals had no history of previous seizures. This improves the accuracy of identifying new-onset seizures.

The main limitation of both Paper II and III is the small sample size. In Paper II, only four individuals developed PSE after EVT restraining the evaluation of brain injury markers in the prediction of PSE. Further, the classification into different subgroups (single seizure, epilepsy, and PSE) in paper III made the evaluation of concentrations difficult as the groups became smaller. Future studies are needed for further investigation.

In Paper III, brain injury markers were collected in individuals after a first-ever seizure, who therefore were at a high risk of epilepsy. While the study allowed investigation of brain injury markers to predict seizures and new-onset epilepsy, the study design did not control for the number of seizures and the correlation with brain injury marker concentrations. Multiple factors could have affected the concentrations of the investigated brain injury markers, such as previous trauma to the head, dementia, etc. Additionally, ASM prescription affects the concentration of brain injury markers (116), but no controlling was done for this.

Summary of main findings

This thesis compiles four studies investigating new PSE risk factors, including the risk of PSE after EVT, with different methodological approaches. One major finding was that individuals with a first-degree relative with epilepsy had a higher risk of PSE. Having a family history increased the PSE risk also in several models adjusting for potential confounding factors. The findings should not be explained by a higher familial risk of stroke or the inclusion of provoked seizures.

Stroke severity was a predictor of PSE also in this material, and it was noted that the impact of family history was more substantial in milder strokes. It seems that family history contributes to PSE risk to a certain degree (depending on other PSE risk factors), which would only be evident in large materials. Presumably, the injury caused by the stroke and genetic susceptibility has a cumulative effect (117). Because Paper I used nationwide data to assess epilepsy diagnoses with similar results in several analyses, we could identify family history to be a risk factor for PSE.

Another main finding in the thesis was that PSE risk was lower after EVT compared to no acute treatment using nationwide register data. The results were consistent in analyses adjusted for age and stroke severity. EVT was associated with a reduced risk also in sensitivity analyses. Individuals selected for EVT are at greater risk of PSE because of high stroke severity and cortical involvement (69, 118), suggesting that EVT has a great impact on PSE prognosis.

Results in relation to previous studies

Family history on PSE risk

In Paper I, a family history was ascertained in 8.6% of stroke cases, comparable with 9.1% in earlier observations by Bianchi et al. (37). The Bianchi group found that the impact of family history is greater before 14 years of age and in epilepsy in general. Some effect of family history was also seen in cryptogenic epilepsy and symptomatic epilepsy, where PSE might be included.

When the impact of family history was studied in individuals up to age 40, the results conflicted on the risk of idiopathic, cryptogenic epilepsy, or focal epilepsies with structural/metabolic or postnatal cause (where PSE might be included) (38, 119). However, direct comparison is difficult because of different epilepsy classifications and because PSE was not explicitly studied.

One study has found associations between having a family member with epilepsy with either acute symptomatic seizures or PSE (41), whereas other studies have not found such association (42, 43, 45). A possible explanation for previous negative findings could be the different methodological approaches, mainly in how the diagnoses were obtained. Assessment of family history by questionnaires or history taking might result in many missing diagnoses because of recollection bias or loss of follow-up. This might be illustrated in the Bianchi study that, compared to our results, reported lower rates of ascertained family history for the subgroups “focal” (6.2%) and “symptomatic” (5.4%) epilepsy. The lower rates of reporting could imply some missing cases when using questionnaires to identify relatives medical history, and is a likely explanation for why the effect of family history was not so evident in their study.

PSE risk after EVT

The PSE incidence of 5.7% after EVT in Paper IV stands in line with or is lower than the general PSE incidences of 6.7% (8) in ischemic stroke. This finding is consistent with that of Alemany et al., who found a five-year PSE incidence after EVT in 8.9% (120). The slightly higher incidence could be explained by the inclusion of younger individuals with more severe stroke.

Another aim of Paper IV was to identify risk factors that could modify PSE risk in EVT. No visible signs of infarction on CT on day one were associated with a lower PSE risk, implying that successful treatment reduce PSE risk, most likely because of limited injury from the stroke (121). This is in agreement with the findings in Paper II with few PSE cases, in which individuals had severe stroke, but also high rates of reperfusion (90%) and low post-treatment NIHSS scores (median 2, range 0 – 10), indicating successful treatment.

Moreover, IVT before EVT was associated with a lower PSE risk in Paper IV. This association was also illustrated in the Alemany study (120). The results are likely to be related to increased recanalization grade when administrating IVT in addition to EVT. Concomitant administration of IVT and EVT is associated with a high degree of successful recanalization and favorable outcome (122), suggesting an additive effect. Altogether, a reduced injury from the stroke illustrated by no signs of infarction on day one after EVT and successful treatment seems to reduce PSE risk.

Another possible explanation for the decreased risk when IVT was given in addition to EVT is that treatment is given within 4.5 h after the onset of symptoms. Therefore, it is likely that this group received reperfusion therapy faster compared to individuals receiving EVT only. Previous Swedish national guidelines on stroke care recommended EVT from 0 to 6 hours after symptom onset, but EVT had proved superiority up to 24 hours compared to standard care alone in 2018 (123, 124). The longer time window was advocated for up to approximately 24 hours in the new Swedish guidelines in 2019 – 2020 (125) and has shown noninferiority with regard to functional outcome and mortality compared to early window EVT (<6 hours) also in the clinical setting in Sweden (113). Before implementing the new guidelines, EVT was performed off-label for up to 24 hours in selected individuals.

Enrollment of individuals in Paper I and IV was earlier than 2018, so faster reperfusion might not fully explain the differences in decreased PSE risk when combining IVT with EVT. Another possible explanation for the lower PSE risk when IVT was given in addition to EVT could be the direct pharmacological properties of IVT. However, this was not evident in Paper IV - the IVT group did not have a decreased risk of PSE compared to no acute treatment. Regarding IVT on PSE risk, IVT alone does not increase the risk (126). This is also true when compared with conservative treatment (127) or with antiplatelet therapy (128).

Since the aim of Paper IV was to explore potential factors that might modify PSE risk in EVT, the contribution of secondary hemorrhage was investigated because a transformation is associated with an increased risk of ASS or PSE (62). Notably, secondary hemorrhage was only found to be a risk factor for PSE in univariate analyses and not in multivariate analyses, consistent with previous findings (120). It seems that EVT is a greater predictor of PSE risk than hemorrhagic transformation, which further favors EVT.

Regarding the low PSE incidence in Paper II, possible explanations could be related to the high rate of recanalization and to cerebral blood supply (108). Included individuals were monitored following a strict protocol to optimize blood pressure during and after EVT. Both optimized blood pressure and a high rate of recanalization could explain the low PSE incidence. There are several reasons why cerebral blood supply can alter the risk of PSE. First, circulatory autoregulation is affected in ischemic stroke. Simultaneously, the tissue at risk is sensitive to small changes in blood pressure - a fall over 40 mm Hg in (MAP) results in a worse functional outcome (121), possibly by worsening collateral blood supply (129), resulting in increased infarction volumes (130). Second, hypocapnia might cause vasoconstriction (131). Third, post-treatment blood pressure is associated with decreased functional outcome and the development of intracerebral hemorrhage (132). Fourth, there is a risk of reperfusion syndrome, which is associated with seizures and an increased risk of secondary bleeding (133). Presumably, a decreased PSE risk could be achieved by closely monitoring the blood pressure during EVT.

Brain injury markers

NfL as a marker of stroke severity and neurodegeneration

In Paper II, the concentrations of the brain injury markers were generally increased in the PSE group that had higher admission NIHSS, indicating that NfL biochemically reflects stroke severity. That NfL reflects the extent of the neuronal damage secondary to stroke has been suggested before (88, 134). Further, acute stroke have been associated with subsequent brain atrophy (135).

In Paper III, NfL concentrations were increased in the PSE group. The increased concentrations of NfL in our data give some pathological insight. Neurodegeneration after stroke could be one mechanism in the PSE epileptogenesis which is supported by increased NfL in drug-resistant epilepsy (93). A correlation between epilepsy and neurodegeneration is also supported by post-mortem studies of accelerated brain aging in chronic epilepsy specimens (136).

The use of NfL in PSE can be implicated by NfL increase due to other neurodegenerative diseases. In traumatic brain injury, concentrations are elevated up to 30 days or even up to 5 years (134). The prolonged elevation of NfL might complicate the use in the prediction of PSE in individuals with previous head trauma. The clinical use of NfL in PSE can further be problematic due to its increase with age (90). It is not known whether NfL solely reflect neurodegeneration or is also reflecting processes involved in the epileptogenesis. Future studies have to investigate the use of NfL in PSE. If future studies cannot confirm NfL to be a suitable prognostic marker for PSE, NfL could perhaps serve as a marker of disease progression and treatment efficacy in PSE similarly to what has been suggested for Downs syndrome and multiple sclerosis (90, 137).

Brain injury markers in the prediction of seizures

The high S100B in the epilepsy group in Paper III implies that this brain injury marker might be useful in predicting new-onset epilepsy after a first seizure. S100B is an astrocytic marker, but the exact contribution of astrocytes in epilepsy is not fully understood. Increased concentrations of S100B have been demonstrated in focal epilepsy, and ASM use alters the concentrations (116), supporting a correlation of S100B in seizures. One possible explanation for the elevation of S100B is that if the Blood-Brain Barrier (BBB) disrupts, neuron-protective astrocytes become activated in response to injury to maintain a stable extracellular matrix (138). If the astrocytic response falters, this could cause an unstable extracellular matrix with subsequent electrolyte changes interfering with seizure generation. Another role of astrocytes in epilepsy could be related to the function of astrocytes to regulate glutamate release which is necessary for neuronal transmission (139, 140).

In our data, GFAP, NSE and tau was not increased in the epilepsy group or in the PSE group. GFAP concentrations were found to depend on age and were only increased in the PSE group before age adjustment. Possibly, GFAP may only be used in specific age groups to predict seizures (91). Similar to our results, no significant difference in NSE have been found in children with epilepsy (91). NSE might also be difficult to use in the clinic because of its sensitiveness to hemolysis and possible alteration due to ASM use (85).

In summary, it seems that markers of astrocytic activation or injury may be more fitting to predict seizures. Perhaps because astrocytic markers reflect a response to injury, which might be involved in the epileptogenesis, while the neuronal markers instead reflect the damage caused by the stroke. It is evident that the timing of acquisition of blood injury markers is important, and more extensive prospective studies should examine this.

Implications for management

After a stroke, individuals should have a follow-up for secondary prevention, either in primary care or in a specialist clinic. In cases where a seizure is recognized, individuals should be referred to a neurologist according to the new Swedish National guidelines (141). No specific programs exist for individuals with a high risk of poststroke epilepsy. Knowledge of risk factors for PSE among health care practitioners is of great importance in the identification of seizures after stroke.

From a clinical perspective, the increased risk in the presence of a positive family history is small compared to other risk factors (e.g. severe stroke or hemorrhagic stroke), but the results nonetheless contribute additional knowledge to the understanding of PSE pathogenesis.

The superiority of EVT is already established. The findings from Paper II and IV do not call for a change in management of individuals with large vessel occlusion receiving EVT with regard to PSE risk. However, long-term risk should be readily characterized because of a rapid increase in the number of performed EVT (18). Since EVT was associated with a reduced risk of PSE, an increased number of performed EVT could also be beneficial regarding the decreased PSE risk. In reality, other factors such as availability and trained neuro-interventionists will limit the number of performed EVT. We found that concomitant IVT reduced PSE risk. However, in a clinical setting, it is evident that the risk of secondary hemorrhage must be evaluated before the administration of IVT.

The results from paper II indicate that optimal blood pressure during EVT resulted in few PSE cases. If further studies could verify these findings, strict blood pressure protocols during EVT could possibly reduce PSE incidence.

Conclusions

To date, it is not possible to prevent PSE development, but finding additional risk factors might help in identifying individuals at high risk. The identification of high-risk individuals would enable appropriate follow-up regimes and facilitate studies on preventive treatment.

Having a family member with epilepsy was identified to increase PSE risk. Family history contributed to an increased PSE risk, but other risk factors such as hemorrhagic stroke and stroke severity remain primary predictors of PSE. Revealing family history as a PSE risk factor adds to the understanding of PSE pathogenesis and could, in the future, contribute to a more individual risk assessment after stroke.

This thesis has also contributed to knowledge on PSE risks after endovascular treatment. The risk of PSE was almost doubled after no acute treatment compared to EVT two years after stroke. Severe stroke was also a strong predictor of PSE risk after EVT. The benefit of EVT is well-established, and with an increasing number of performed EVT, recognition of long-term risk after EVT is important. The results indicate that EVT has favorable long-term outcomes regarding PSE development.

The results from Paper II and III indicated that biochemical assessment of stroke severity is possible in addition to radiologic lesion size and NIHSS scores. Whether biochemical brain injury markers can aid in the prediction and diagnosis of PSE requires further study.

Future Perspectives

Identifying family history as a risk factor for PSE could hopefully inspire future studies on genetics in PSE. Knowledge of PSE genes could pave for studies on tailored preventive treatment. The genetic variations that have been associated with PSE have so far been linked to genes related to oxidative stress and inflammation, suggesting that PSE risk depends on the response after the stroke, which might be reflected by blood-brain injury markers.

Administration of intravenous thrombolysis (IVT) in addition to EVT was associated with a lower PSE risk. Future studies to confirm these findings are welcomed. More precise knowledge of treatment efficacy could improve acute stroke care further with regard to a decreased PSE risk. Additional prospective studies on the influence of intraprocedural factors such as blood pressure during and after EVT on PSE risk could investigate this further.

PSE risk factors most probably differ between hemorrhagic and ischemic stroke, but this was not studied in this thesis and remains to be answered in future studies.

Further studies with high-risk individuals are needed to evaluate the potential of brain injury markers in predicting epilepsy and PSE. An important remaining question is at what time the blood samples should be obtained for an optimal diagnostic utility. Another remaining question is whether the brain injury markers that increase with age are only suitable in specific age groups for diagnostic utility. At last, investigation of the use of the brain injury markers in disease progression or treatment efficacy is warranted.

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