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Risk factors for a first epileptic seizure after stroke: A case control study

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ABSTRACT

Introduction: The risk of seizures increases after stroke, but not all risk factors are known. We aimed to identify factors that increase the risk of a first seizure after a stroke.
Methods: Multicenter case–control study of 161 patients with a first seizure after stroke (105 provoked/acute and 56 unprovoked/remote symptomatic) matched to 279 hospital stroke controls by center, gender, age and timing of stroke.
Results: The risk of first seizure (odds ratio (OR), 95% confidence limits (CL)) was 3.6 (2.4–5.5) for cortical involvement, 2.5 (1.2–5.3) for multiple CT-scan lesions, 2.4 (1.5–3.9) for supratentorial lesions, 2.4 (1.6–3.7) for prior lesions on CT-scan, 2.1 (1.1–4.7) for family history of seizures, 2.0 (1.1–3.6) for use of epileptogenic drugs, 1.7 (1.0–2.9) for large lesions, 1.6 (1.0–2.8) for hemorrhagic lesions, and 1.4 (1.0–2.2) for cortical atrophy. After multivariate analysis, including all the factors significant in univariate analysis, the strongest independent predictor of a first seizure was cortical involvement (OR 3.3; 95% CL = 2.1–5.0), followed by prior lesions (2.2; 1.4–3.4) and hemorrhagic stroke (1.8, 1.0–3.2). The multivariate analysis model for remote symptomatic seizures included cortical involvement, large size, and prior lesions; the model for acute seizures included cortical involvement, alcohol consumption >50 g/day, hemorrhagic stroke, and prior lesions on CT-scan.
Discussion: Cortical involvement, the presence of prior lesions on CT-scan, and hemorrhagic lesion are the most important risk factors for a first-ever seizure after stroke.

1. Introduction

Stroke is the most common cause of epilepsy in the elderly [1]. In the Oxfordshire Community Stroke Project, the cumulative probability of seizures after a first stroke was about 6% at one year and raised to 11% at 5 years, with significant differences across stroke subtypes (cerebral infarction 4 and 10%; primary cerebral hemorrhage 20 and 26%; subarachnoid hemorrhage 22 and 34%) [2]. Camilo and Goldstein [3] reviewed the literature on the risk of seizures in patients with ischemic stroke and found a cumulative incidence of 2–33% for acute symptomatic seizures, 3–67% for unprovoked seizures, and 2–4% for epilepsy. The risk of seizures after ischemic stroke was substantial only in patients presenting with severe strokes due to total anterior circulation infarction. Cortical site, severity and size of the lesion were independent predictors of acute symptomatic seizures. However, the interpretation of the study findings was complicated by their heterogeneous designs, inconsistent uses of terminology, small sample size, different periods of follow-up, and ambiguities in seizure

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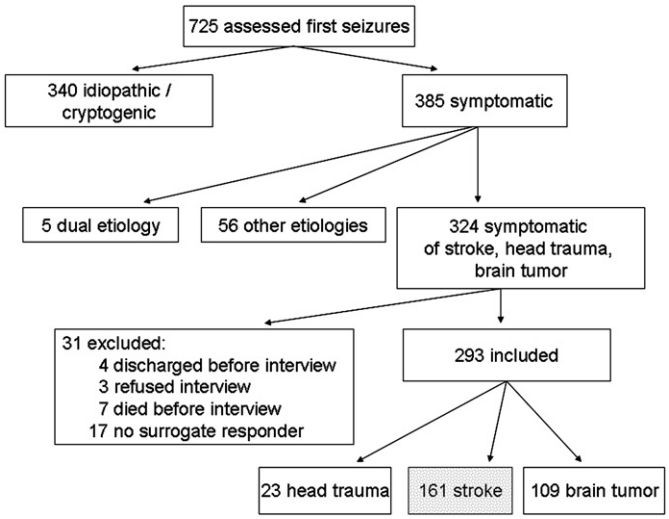

Fig. 1. Flow chart illustrating the enrollment in the main study [4]: 161 cases with a first seizure after stroke are analyzed here.

identification and classification. We performed a study on alcohol use as a risk factor for seizures symptomatic of stroke, brain tumor and head trauma [4] that collected information on several other risk factors. Here we examine stroke patients aiming: 1] to identify factors associated with higher post-stroke seizure risk; and 2] to calculate the magnitude of that risk.

2. Patients and methods

The design of the study has been extensively described [4]. In brief, we observed 725 patients with a first seizure or a first medically evaluated seizure consecutively admitted to one of the participating hospitals. Inclusion criteria were age 15 years or older, having a seizure in the 48 h before hospital admission, evaluation by a neurologist, seizure described by eye witnesses or, for generalized tonic–clonic seizures, at least three of the following criteria: loss of consciousness, urinary or fecal incontinence, laceration of tongue or cheek, and post-ictal confusion or Todd's paralysis [5].

Seizures were classified according to the 1981 proposal for Revised Clinical and Electroencephalographic Classification of Epileptic Seizures [6]. A first seizure was defined as the first seizure (or the first cluster of seizures within a 24-hour period) ever experienced by the patient, excluding febrile seizures; a first medically evaluated seizure was the first seizure ever evaluated by a physician in patients who had had previously unevaluated seizures of any type. We enrolled 340 patients with idiopathic/cryptogenic seizures, and 385 with symptomatic seizures (Fig. 1); 161 of these had a previous stroke and are analyzed here. Stroke was defined according to the WHO criteria [7], as the acute onset of neurological symptoms of presumed vascular origin and >24 h duration. Seizures were divided into provoked (occurring within seven days of the cerebrovascular accident) and unprovoked symptomatic (occurring more than one week after the accident) on the basis of history and clinical examination [8]. Patients with seizures and only CT signs of previous asymptomatic hemispheric stroke were classified as remote symptomatic seizures. In this paper we will use the terms acute symptomatic and remote symptomatic as the equivalent of provoked and unprovoked seizures.

2.1. Controls

We searched two controls for each case from the list of patients admitted to the Emergency Room, with a negative history of epileptic seizures (excluding febrile seizures). The first two controls matching the case were interviewed. Controls were matched to cases according to center, age (±5 years), sex, and timing of stroke. We matched stroke patients with acute symptomatic seizures to controls with stroke occurred in the seven days preceding the interview and stroke patients with remote symptomatic seizures to controls with stroke occurred more than seven days before interview. Controls of patients with remote symptomatic seizures had to have an interval between stroke and study entry at least equal to that of the matched case. The interval was at least six months for controls of cases with only CT signs of previous asymptomatic hemispheric stroke.

2.2. Questionnaire and risk factors

All risk factors were defined, where possible, in accordance with previous reports, to ensure uniform interpretation of the events to be measured: family history of seizures: first-degree relative, first-degree cousin, uncle/aunt, or grandparent affected by at least one afebrile seizure of any type; complications of pregnancy [9]: any complication (toxemia, hemorrhage, nausea) requiring hospitalization longer than two days; low gestational age: birth before the beginning of the 38th week of gestation; low birth weight: weight ≤2500 g; complications of delivery [9]: any of the followings: mechanical complications, abnormal fetal position, coiling of cord, or prolonged delivery; psychomotor retardation: any problem during the first five years of life causing a delay in achieving the milestones of normal development; febrile seizures [10]: seizures occurring between the age of 30 days and 5 years, with no previous afebrile seizure (except neonatal), and associated with fever but with no evidence of intracranial infection or other recognized acute neurological illness; average daily intake of absolute alcohol (ADAA): this was calculated with reference to the six months before inclusion in the study, asking about different beverages separately to obtain a total intake in grams per day [11]; history of cerebral palsy [10]: disorder of movement and posture diagnosed before age 16 years, not attributable to a progressive brain lesion or postneonatal brain injury; epileptogenic drugs: these included iv. penicillin, or aminophylline, antiarrhythmic, antitubercular, tricyclic antidepressants, neuroleptic drugs in the seven days before the seizure or the interview; metabolic alterations at admission: history of diabetes, therapy with insulin or oral hypoglycemic drugs, or hypoglycemia or electrolyte alterations at admission. Diagnoses of history of drug addiction, hypertension, and renal insufficiency were accepted as made by the caring physician. Further information on the preparation and validation of the questionnaire is reported elsewhere [11,12].

2.3. Definition of CT characteristics

One or more CT-scan reports were obtained for all cases and controls and evaluated by two neurologists, blind each other and to the status of case or control. For reports lacking complete information, original images were obtained. A third neurologist decided when the two first neurologists disagreed. The study variables were defined as follows: type of stroke: hemorrhagic vs. ischemic, including hemorrhagic infarction; site of the lesion: supratentorial vs. sub-tentorial and cortical vs. subcortical; patients with both supra- and sub-tentorial lesions or both cortical and subcortical lesions were considered supratentorial or cortical; size of the lesion: large (total anterior circulation infarction [2] or lobar hemorrhage) vs. all the others; number of lesions: none, single or multiple; cortical atrophy, edema, and leukoaraiosis were considered when described in the CT report; prior lesions not related to the current cerebrovascular episode were also considered, when present. For patients with no lesions at CT-scan (11 cases and 36 controls; 31 with stroke occurred in the previous seven days and 16 before), type of stroke was classed as ischemic, and site of the lesion was conservatively classed in the lower risk categories (sub-cortical and sub-tentorial); however, a sensitivity