

# Anger, a Result and Cause of Stroke: A Narrative Review

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Post-stroke mood and emotional disturbances are frequent and diverse in their manifestations. Among them, post-stroke depression is the best known. Although post-stroke anger (PSA) has been studied relatively less, it can be as frequent as depression. Manifestations of PSA range from overt aggressive behaviors (including hitting or hurting others) to becoming irritable, impulsive, hostile, and less tolerable to family members. The possible pathophysiological mechanisms of PSA include neurochemical dysfunction due to brain injury, frustration associated with neurological deficits or unfavorable environments, and genetic predisposition. PSA causes distress in both patients and their caregivers, negatively influences the patient's quality of life, and increases the burden on caregivers. It can be treated or prevented using various methods, including pharmacological therapies. In addition, anger or hostility may also be a risk or triggering factor for stroke. The hazardous effects of anger may be mediated by other risk factors, including hypertension or diabetes mellitus. The identification of anger as a result or cause of stroke is important because strategic management of anger may help improve the patient's quality of life or prevent stroke occurrence. In this narrative review, we describe the phenomenology, prevalence, factors or predictors, relevant lesion locations, and pharmacological treatment of PSA. We further describe the current evidence on anger as a risk or triggering factor for stroke.

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## Introduction

Stroke survivors frequently present with complications of mood and emotional disturbances, including depression, anxiety, and emotional incontinence.<sup>1</sup> Additionally, they often show feelings of anger, angry outbursts, irritation and impulsiveness, and aggressive behavior toward others. The pathogenesis and predictors of this post-stroke anger (PSA) and its relationship with lesion locations remain uncertain. Although the overall negative impact of PSA appears to be less severe than that of post-stroke depression, it still causes distress and embarrassment, decreases patients' quality of life (QOL),<sup>2</sup> and increases caregiv-

er burden.<sup>3</sup> PSA can be treated or prevented by various methods, including pharmacological therapy. However, this important post-stroke symptom has been underdiagnosed, neglected, and understudied.

Furthermore, anger may be a risk or triggering factor for stroke. The hazardous effects of anger may be mediated by other risk factors, including hypertension or diabetes mellitus. The identification of anguish or negative feelings as risk factors or triggers of stroke is important because strategies to manage an individual's anger may prevent stroke occurrence. Thus, anger may be both a result and cause of stroke. In this narrative review, we first describe the phenomenology, prevalence, fac-

tors or predictors, relevant lesion locations, and pharmacological treatment for PSA. We then describe the current evidence on anger as a risk or triggering factor for stroke.

### Strategy for literature search

We selected all pertinent articles published until May 2022, which were related to anger either as a post-stroke symptom or as a triggering/risk factor in stroke development, from the following databases: MEDLINE, PubMed, Index Medicus, Web of Science, Embase, CINAHL, SCOPUS, and Cochrane. Anger, anguish, anger proneness, emotional upset, impulsiveness, aggression, aggressive behavior, irritability, and hostility were used as search items. Relevant articles dealing with the above items were examined and included in this review, when necessary. We included only articles written in English.

In this search, we identified 4,231 articles (PubMed 360, CINAHL 38, Cochrane 54, MEDLINE 141, Scopus 1,132, Embase 1,204, Index Medicus 24, and Web of Science 1,278). Among them, 1,533 duplicate and 2,657 irrelevant articles were removed after reviewing the titles, abstracts, and details. Eight articles were included after a manual search. Consequently, 49 articles were finally included in this study, wherein 36 were related to PSA and 13 to anger as a risk or triggering factor. The details of the screening process are shown in Figure 1.

### Anger as a result of stroke

#### Phenomenology and terminology

Patients with acute stroke often exhibit aggressive behavior, including hitting or hurting others, kicking, biting, grabbing, pushing, and throwing objects. Their verbal behavior may include cursing, screaming, or hostile muttering. In some cases, these behaviors are one of the broad manifestations of delirium<sup>4</sup> that include disturbances in attention, awareness, and cognition. Studies have also described a so-called "catastrophic reaction,"<sup>5,6</sup> which is a constellation of symptoms including anxiety reactions, tears, aggressive behavior, refusal, and swearing.<sup>5</sup> Typically, catastrophic reaction is present in patients with aphasia and elicited when the examiners ask the patients to do something that they find difficult to perform.<sup>6</sup> It remains uncertain whether these delirious behaviors and catastrophic reactions are truly related with patients' anger. With the concomitant presence of delirious or aphasic symptoms, it is impossible to perform the formal, standardized assessment of anger (see below). Moreover, these behaviors generally subside over time along with the disappearance of other delirious or aphasic symptoms.<sup>4,5</sup> Thus, the aggressive behaviors shown in these patients are unlikely to be an anger based on true emotion disturbances.

Therefore, we did not include these behaviors in this review. Instead, we discussed purely aggressive behaviors associated with anger in patients with stroke. Compared with their pre-

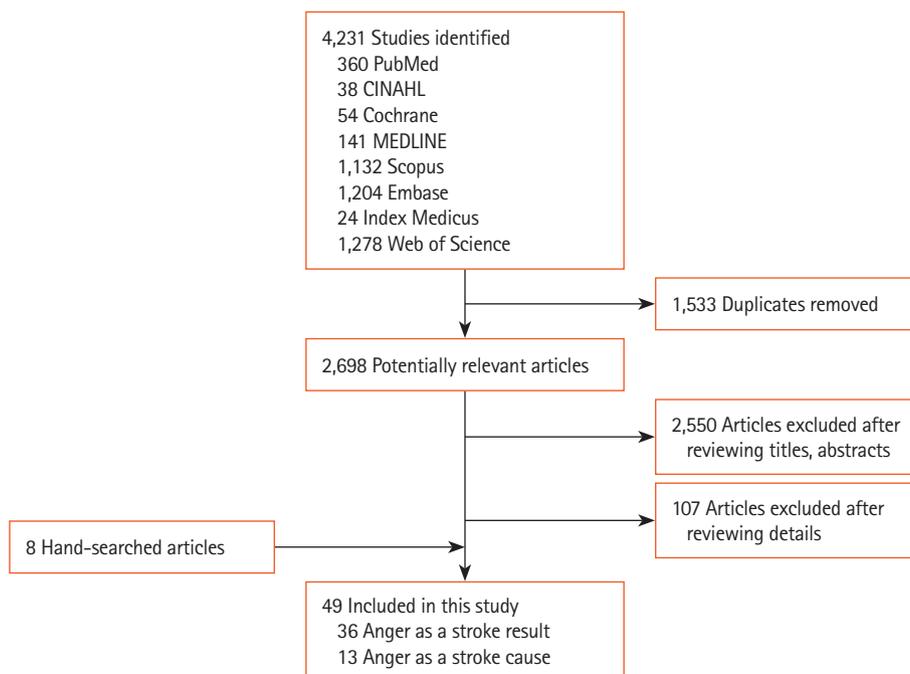


Figure 1. Flow diagram depicting the selection process of the studies included in this review.

morbid state, these patients become irritable, impulsive, hostile, and less tolerable and exhibit uncontrollable anger. They often express excessive anger at their spouse and other family members regarding trivial matters that would not have evoked anger in their pre-stroke stage.<sup>7</sup> These symptoms have been previously described as "the inability to control anger or aggression"<sup>7</sup> or "post-stroke anger proneness."<sup>8</sup> Here, we will use a simpler and broader term, PSA.

## Methods to assess PSA

Unfortunately, no standardized method exists for assessing PSA levels. Some studies have used the 10-item Spielberger Trait Anger Scale (see below). For each question, the patients are asked to use a numerical scale (1, almost never; 2, sometimes; 3, often; and 4, almost always) to best represent their status. An overall anger score can be obtained by summing the individual scores.<sup>7</sup>

The 10-item Spielberger Trait Anger Scale

1. I am quick-tempered.
2. I have a fiery temper.
3. I am a hotheaded person.
4. I get angry when I am slowed down by others' mistakes.
5. I feel annoyed when I am not given recognition for doing good work.
6. I fly off the handle.
7. When I get angry, I say nasty things.
8. It makes me furious when I am criticized in front of others.
9. When I get frustrated, I feel like hitting someone.
10. I feel infuriated when I do a good job and get a poor evaluation.

Because patients may have had anger before stroke occurrence, whether their anger was newly developed or increased in intensity after stroke needs to be identified. Thus, investigators compared the anger scores after stroke with those before stroke occurrence reported by the patients.<sup>7,9</sup> Because this requires patients' intact memory and reliable response, this approach may be possible only in patients with relatively intact memory in the acute or subacute stage of stroke but not in those who experienced stroke long ago.

One study<sup>10</sup> utilized the Present State Examination, and patients were identified as 'aggressive' based on positive ratings of one or more of the following five items: (1) the patient acknowledges showing anger by shouting or quarreling (1 point), hitting people, throwing or breaking things (2 points); (2) the patient showed a discrete episode of violent behavior that had a catastrophic impact on others (e.g., significant bodily injury) (2 points) or more than one discrete episode of violence (3

points); (3) the patient showed hostile behavior to the examiner through anger, irritability, or overt aggression (1 point); (4) the patient showed agitation during the interview (1 point); or (5) the patient showed gross excitement or violence during the interview (1 point). These behaviors were reported by the patients, family members, or hospital staff members. An "aggression sub-score" may be calculated from these five items, with eight as the maximum score.

Another study<sup>2</sup> employed the Neuropsychiatric Inventory-Carers Distress Version, which is an informant-rated scale that measures 12 domains: delusion, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/liability, motor disturbance, nighttime behavior, and appetite.

Caregivers (e.g., family members or nurses in the residential facility) are first presented with a screening question, "Does the patient have periods when he/she refuses to cooperate or will not let people help him/her? Is he/she difficult to handle?" If the caregivers responded positively ("yes") to the screening question, they are then asked to respond to eight additional questions aimed at quantifying the severity of agitation/aggression over the previous month. Positive responses to the screening question and at least one of the eight questions are required to confirm agitation/aggression. These questions can be divided into "passive" or "active" aggression categories, as shown below:

- Passive 1. Does the patient get upset with those trying to care for him/her or resist activities, including bathing or changing clothes?
- Passive 2. Is the patient stubborn and wants to have things in his/her way?
- Passive 3. Is the patient uncooperative and resistive to help from others?
- Passive 4. Does the patient have any other behavior that makes him/her difficult to handle?
- Active 5. Does the patient shout or curse angrily?
- Active 6. Does the patient slam doors, kick furniture, or throw objects?
- Active 7. Does the patient attempt to hurt or hit others?
- Active 8. Does the patient have any other aggressive or agitated behavior?

In another study,<sup>11</sup> items that assessed anger, hostility, and aggression from several scales were used. From the Catastrophic Reaction Scale,<sup>12</sup> items 5 (patient behaved angrily), 6 (patient complained of feeling angry), 7 (patient swore), and 8 (patient expressed displaced anger) were selected. From the Mania Rating Scale,<sup>13</sup> items 5 (irritability) and 9 (disruptive-aggressive behavior) were chosen. Items 4 (hostile feelings) and

43 (hostility) of the Comprehensive Psychopathological Rating Scale<sup>14</sup> were also used. Patients were classified into "no anger" group if they scored 0 in all the selected items and into "anger" group, if not. Other rating tools used were the Emotional Behavior Index<sup>15</sup> and Emotional and Social Dysfunction Questionnaire.<sup>16</sup>

## Prevalence

The studies that investigated PSA prevalence are summarized in Table 1. In the acute stage of stroke (i.e., when patients are admitted to a hospital), PSA or aggressive behaviors occurred in 11% to 35% of the patients.<sup>9-11,15</sup> In the subacute stage (3 to 12 months after stroke onset), the prevalence was 19% to 32%.<sup>2,7</sup> Thus, despite the different study settings and diagnostic tools used, PSA appears to be relatively common during both the acute and subacute stages of stroke. Although PSA prevalence in the chronic stage of stroke has been rarely studied, a recent study<sup>17</sup> investigated the long-term change in anger score in patients with stroke. It was found that the average anger score measured by the Spielberger Trait Anger Scale was 22.9 at the acute ( $\leq 21$  days after onset) stage of stroke, 21.6 at 6 months post-stroke, and 16.2 at long-term follow-up (average 5 years). Thus, after the acute/subacute stage of stroke, anger symptoms seem to gradually decrease over time.

Noh et al.<sup>3</sup> studied 23 patients (mean age, 55 years) with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Among all patients, 18 patients had an ischemic stroke, two had intracerebral hemorrhages, one had both ischemic stroke and intracerebral hemorrhage, and two had transient ischemic attacks. PSA was detected in five patients (22%).

## Associated factors and lesion locations

Although young age and male sex have been reported as factors associated with PSA,<sup>16,18</sup> the results were not replicated in other studies.<sup>7,9,11</sup> A study showed that in the acute phase of stroke, PSA was independently related to the presence of previous stroke, the National Institutes of Health Stroke Scale (NIHSS) score, and monoamine oxidase A (MAO-A) polymorphisms associated with low activity.<sup>9</sup> In the subacute stage, motor dysfunction and dysarthria<sup>7</sup> and diabetes mellitus<sup>2</sup> were found to be associated with PSA. PSA has also been shown to be associated with depression.<sup>2,10,19</sup> However, in a study assessing both depression and emotional incontinence, PSA was more closely associated with emotional incontinence than depression.<sup>7</sup>

The relationship between stroke lesion location and PSA remains unclear. One computed tomography scan study<sup>19</sup> report-

ed that left hemispheric lesions and lesions located more proximal to the frontal cortex were associated with aggressive behavior. However, the patient number ( $n=10$ ) was too small for a definitive conclusion. Kim et al.<sup>7</sup> analyzed brain lesions mostly using magnetic resonance imaging (MRI) and emphasized that PSA was closely associated with lesions involving the fronto-lenticulocapsular-pontine base area. Patients with lesions involving other areas, including the parietal, occipital, and cerebellar regions, rarely exhibited PSA. Another MRI study showed that PSA was closely associated with ventral pontine and lateral cerebellar infarcts.<sup>20</sup> Conversely, other studies<sup>10,11</sup> found no relation between stroke lesion location and PSA. However, in these studies, the lesion location was categorized more crudely. In one study, the severity of white matter hyperintensities was not associated with PSA.<sup>20</sup>

## Pathophysiology

Considering that PSA is related to the NIHSS score,<sup>9</sup> motor dysfunction, and dysarthria,<sup>7</sup> it may partly be a normal reactive response secondary to the patient's neurological disabilities. One study<sup>7</sup> specifically asked 47 patients with PSA about the main reason for them getting angry, and 28% of them stated that their anger was caused by their neurological deficits. Furthermore, patients stated that their anger was provoked by family members (15 patients), colleagues at work (four patients), and unfavorable economic conditions (four patients). These observations, along with recent studies that showed a relationship between the lack of social support and PSA<sup>17</sup> and between PSA and depression,<sup>2,10,19</sup> suggest that PSA might be a manifestation of depression or frustration in patients with stroke.

However, in the discussed study, 23% of patients stated that their anger occurred spontaneously without any specific reasons.<sup>7</sup> Spontaneous anger/aggression was also observed in most patients with provoked anger. Moreover, no differences were found in the frequency of motor dysfunction between patients with spontaneous anger and those with provoked anger. Finally, although PSA may be related to depression,<sup>2,10</sup> the discussed study<sup>7</sup> showed that only 15% of the patients with PSA had depression, which was not different from the depression rate of patients without PSA (12%). Moreover, PSA was more closely related to emotional incontinence,<sup>7</sup> a symptom presumably caused by neurochemical dysfunction secondary to a brain lesion,<sup>1</sup> than depression. Thus, PSA may at least partly be a symptom related to brain injury itself, even in patients with physical disabilities. Although not unanimously agreed upon, PSA may be related to frontal-lenticular-pontine base lesions, which is also related to emotional incontinence.<sup>7</sup> Therefore, PSA may be caused by the disinhibition of impulse

**Table 1.** Summary of the studies on post-stroke anger

Study	Terminology	Stroke subtype	Number	Time from stroke onset	Tools	Definition of anger	Prevalence	Associated factors
Paradiso et al. (1996) <sup>19</sup> USA	Aggressive behavior	CI and ICH	309	Mean, 14 days	Structured interview	Patients who experienced feeling of anger or reported that they had quarrel, shout, hit people, break things	6%	Young age Depression Cognitive impairment Less impaired daily living activities Lesion in left hemisphere Proximal to the frontal cortex
Kim et al. (2002) <sup>7</sup> South Korea	Inability to control Anger or aggression	CI and ICH	145	2–13 mo	10-Item Spielberger Trait Anger Scale	1. Post-stroke anger score > prestroke anger 2. Patient felt that he/she develops PSA 3. At least one relative agrees with (2)	32%	Motor dysfunction Dysarthria Emotional incontinence
Chan et al. (2006) <sup>10</sup> USA	Aggressive behavior	CI and ICH	92	<6 mo	Present State Examination	Positive ratings on 1 or more of the following 5 items: 1. Patient acknowledges showing anger by shouting or quarrel (1 point), or by hitting people or throwing or breaking things (2 points) 2. Discrete episode of violent behavior that had an impact on others (e.g., body injury) (2 points) or more than 1 episode of violence (3 points) 3. Hostile behavior to examiner through anger, irritability, or overt aggression (1 point) 4. Agitation during an interview (1 point) 5. Gross excitement/violence during interview (1 point)	25%	Anterior edge of lesion Closer to the frontal pole Depression Anxiety Cognitive impairment
Santos et al. (2006) <sup>11</sup> Portugal	Anger	CI, ICH, and SAH	202	≤4 days	8 Items from three psychiatric scales Catastrophic Reaction Scale Mania Rating Scale and Comprehensive Psychopathophysiological Rating Scale	If the patient scored at least 1 point in any of those items	35%	
Choi-Kwon et al. (2013) <sup>9</sup> South Korea	Anger proneness	CI	508	Acute stage	10-Item Spielberger Trait Anger Scale	1. Post-stroke anger score > prestroke anger 2. Patient felt that he/she develops PSA 3. At least one relative agrees with (2)	15%	Presence of previous stroke NIHSS score low MAO-A activity
Noh et al. (2014) <sup>3</sup> South Korea	Anger proneness	CADASIL patients	23	ND	10-Item Spielberger Trait Anger Scale	1. Post-stroke anger score > prestroke anger 2. Patient felt that he/she develops PSA 3. At least one relative agrees with (2)	22%	

Table 1. Continued

Study	Terminology	Stroke subtype	Number	Time from stroke onset	Tools	Definition of anger	Prevalence	Associated factors
Lau et al. (2017) <sup>2</sup> Hong Kong	Aggression	CI	324	3 mo	Interview with a caregiver with Neuropsychiatric Inventory-Carers Distress Version 12 domains: delusion, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/liability, motor disturbance, night time behaviors, and appetite	The screening question followed by 8 further questions (see the text)	19%	Diabetes Depression
Kwon et al. (2021) <sup>17</sup> South Korea	Anger	CI and ICH	222	Acute stage 6 mo and 5 yr	10-Item Spielberger Trait Anger	Simply assessed average anger score	22.9 at admission 21.6 at 6 mo 16.2 at 5 yr	

CI, cerebral infarction; ICH, intracerebral hemorrhage; PSA, post-stroke anger; SAH, subarachnoid hemorrhage; NIHSS, National Institutes of Health Stroke Scale; MAO-A, monoamine oxidase A; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; ND, not described.

control secondary to brain injury. As selective serotonin reuptake inhibitors (SSRIs) are effective in the management of PSA (see below), serotonergic dysfunction due to brain lesions has been suggested to induce PSA.<sup>1</sup> One study suggested that the brain serotonin system may work differently between "anger trait" and "state condition of anger."<sup>21</sup>

Other studies have suggested that PSA may be associated with personality changes due to frontal lobe lesions, which result in increased aggression or exacerbation of preexisting aggressive behavior.<sup>10</sup> Along with the association between cognitive impairment and PSA, patients may also have anger due to frustration associated with impaired ability to communicate, inappropriate response to stimuli (including pain or noise), or misinterpretation of a caregiver's action.<sup>10</sup> PSA may present as a manifestation of "behavioral and psychological symptoms" of vascular cognitive impairment (VCI). One study showed that 40% of patients with VCI exhibited agitation/aggression. These patients usually had multiple or diffuse cerebral infarcts, and their anger was mostly associated with cognitive impairment and other neuropsychiatric symptoms, including depression.<sup>22</sup>

Finally, PSA may have a genetic predisposition. One study<sup>23</sup> based on the genotyping of serotonin-synthesizing tryptophan hydroxylase 2 (*TPH2*) genes (rs4641528 and rs10879355) in the genomic DNA of 383 patients with stroke demonstrated that post-stroke depression (95% confidence interval [CI], 1.039 to 5.631;  $P < 0.05$ ) and emotional incontinence (95% CI, 1.029 to 11.678;  $P < 0.05$ ) were related to the *TPH2* rs4641528 C allele. However, PSA was not related to any of these factors. Instead, it was related to MAO-A polymorphisms associated with low MAO-A activity.<sup>9</sup> This observation is in line with a previous study that showed polymorphic variation in the *MAO-A* gene was related to dysfunctional central nervous system serotonergic responsivity, which in turn results in individual variability in aggressiveness and impulsivity.<sup>24</sup> Although the detailed mechanism linking PSA to genetic disturbances remains uninvestigated, these heterogeneous genetic characteristics may partly explain the reason why a particular group of patients exhibits PSA among patients with brain lesions at a similar location.

One of the limitations of PSA research is the rare use of control participants (i.e., participants without stroke). A study by Santos et al.<sup>11</sup> found no differences between the frequency of anger in patients with stroke (35%) and in those with acute coronary syndrome (38%). This observation contradicts the theory that PSA is directly caused by brain lesions. As anger is considered a risk factor for stroke,<sup>25,26</sup> the anger observed in patients with stroke may not be a real "post-stroke" anger. However, previous studies using controls are too rare to obtain a definitive conclusion. Patients with PSA stated that their an-

ger after stroke increased when compared to their pre-stroke anger.<sup>7,9</sup> Moreover, a long-term follow-up study showed a gradual decrease in PSA intensity over time.<sup>17</sup> Thus, the notion that anger is a result of stroke seems to be reasonable.<sup>27</sup> PSA appears to be a multi-factorial phenomenon related to neurochemical change secondary to brain damage, reactive behavioral changes associated with functional deficits or unfavorable environments, psychiatric manifestation of VCI, and possibly, genetic polymorphisms involving MAO-A activity.

### Impact on patients' quality of life and caregiver burden

The impact of PSA on patients' clinical outcomes and QOL has rarely been studied. One study<sup>2</sup> investigated the association of PSA with patients' QOL and found that patients with PSA had lower QOL total scores and Personality Changes and Social Role scores than those without PSA. They further categorized PSA into "passive aggression" and "combined passive and active aggression" and found that the combined passive and active aggression group had significantly lower Energy and Thinking scores on the QOL questionnaire than the passive aggression group. Another study showed that patients' anger was one of the challenging items for caregivers of stroke survivors.<sup>28</sup>

Another study involving patients with CADASIL<sup>3</sup> assessed QOL using the stroke-specific QOL scale (49 items comprising 12 domains),<sup>29</sup> while caregivers' burden was evaluated using the Sense of Competence Questionnaire (27 items).<sup>30</sup> Considering the small number of patients, emotional incontinence was combined with PSA and categorized as "non-depressive emotional disturbances" (NDED). Similar to depression, NDED negatively affected caregivers' burden. Although QOL scores were low in both patients with depression and in those with NDED, the difference was statistically significant only in patients with depression. This indicates that although NDED was associated with poor QOL, its impact was relatively mild compared to that of depression. It seems that patients' anger may occasionally trouble their caregivers and increase their burden. However, unlike depression, however, NDED is usually episodic and not associated with persistent, inherent psychological problems, which may explain the relatively weaker influence of NDED on a patient's subjective QOL assessment. Nevertheless, these results should be interpreted cautiously because the authors had examined NDED (combination of emotional incontinence and anger) and not PSA alone.

### Treatment

Antidepressants including fluoxetine<sup>31</sup> and citalopram<sup>32</sup> are beneficial in treating aggressive behavior in patients with per-

sonality disorders and dementia, respectively. However, pharmacological trials have rarely been conducted in patients with PSA. One study<sup>10</sup> showed that compared to the placebo, antidepressants, including fluoxetine (up to 40 mg/day) or nortriptyline (up to 100 mg/day), did not significantly lower anger scores. However, the patient number was too small (13 in placebo and seven in treatment group) to draw reliable conclusions. In another study, Choi-Kwon et al.<sup>8</sup> enrolled 152 patients with post-stroke depression, emotional incontinence, or PSA, wherein the PSA levels were assessed using the Spielberger Trait Anger Scale. Patients were randomized to receive either fluoxetine 20 mg/day or a placebo for 3 months, with follow-up evaluations conducted at 1, 3, and 6 months after treatment initiation. The primary outcome was the PSA score at each follow-up assessment, while the secondary outcome was the percentage change in the scores. In patients with PSA (n=95), the demographic characteristics and mean PSA score at enrollment did not differ between the fluoxetine and placebo groups. At 3 months, the mean PSA score was significantly lower in the fluoxetine group than in the placebo group ( $P<0.01$ ). However, after the discontinuation of the study medication (at 3 months), the PSA score tended to increase in the fluoxetine group. The percentage changes in PSA scores were also significantly greater at 3 months after treatment.

In another study, Kim et al.<sup>33</sup> randomized 478 admitted patients with ischemic stroke (<21 days after stroke onset) to receive a placebo (n=237) or escitalopram (10 mg/day, n=241). The primary endpoint was the frequency of moderate or severe depressive symptoms (Montgomery-Åsberg Depression Rating Scale score  $\geq 16$ ) at 3 months post-stroke. The effect on PSA (measured using the Spielberger Trait Anger Scale) was one of the secondary endpoints. According to the prespecified protocol, efficacy endpoints were primarily analyzed with the full analysis set (including all randomly assigned participants who took at least one dose of the study medication and underwent at least one primary endpoint assessment). The results showed that the mean anger score measured at 3 months post-stroke was significantly lower in the escitalopram group than in the placebo group (20.2 vs. 21.3,  $P=0.035$ ). Escitalopram was generally well tolerated, although diarrhea incidence was more common in the escitalopram group (4%) than in the placebo group (1%).

Thus, SSRIs are generally tolerable and effective in reducing PSA severity and can be considered first-line drugs for PSA. Additionally, SSRI use in patients with emotional disturbances was found to improve their QOL.<sup>34</sup> Other studies showed that beta-adrenergic antagonists<sup>35</sup> and lithium<sup>36</sup> may reduce aggressiveness in patients with brain injury. Therefore, these

drugs may be used for patients who do not respond satisfactorily to SSRIs. However, it should be noted that no clinical trials of these drugs have been conducted on patients with stroke.

In the acute stage of stroke, neuroleptics (either haloperidol or atypical neuroleptics) may be used in patients with severe aggressive behavior<sup>37</sup> to prevent harm to the patients and surrounding people. The dose can be titrated according to the controllability of aggression and intensity of adverse effects. Adverse cardiovascular effects and the possibility of lowering the seizure threshold should also be considered in patients with stroke. After controlling for acute aggressive behavior, the dose should be gradually reduced and eventually discontinued.

The role of psychiatric or psychological counseling in PSA management remains unclear. One study showed that patients with stroke often have anger that is provoked by family members or colleagues,<sup>7</sup> while another study<sup>17</sup> found a relation between the lack of social support and PSA in the chronic stage of stroke. These observations suggest that successful PSA management may have to include psychological intervention or proper education for patients and caregivers. However, evidence of the benefits of such non-pharmacological therapy for PSA is currently extremely low.<sup>38</sup>

## Anger as a cause of stroke

### Anger as a risk factor for stroke

In 1999, Everson et al.<sup>25</sup> followed Finnish male patients for 8.3 years and found that participants with the highest level of expressed anger had double the risk of stroke than those with the lowest level of expressed anger (Table 2). In another study involving 13,851 men and women (aged 48 to 67 years) from white and black populations who were followed up for 6.4 years, trait anger was reported to be modestly associated with stroke risk. Additionally, heterogeneity was observed in the effects of age and high-density lipoprotein cholesterol (HDL-C) level. Although anger traits were significantly associated with stroke risk among young ( $\leq 60$  years) participants and those with high HDL-C levels, no such association was found among older participants or those with lower HDL-C levels.<sup>26</sup> Another large epidemiological study ( $n=10,366$ ) reported a similar result, wherein unhealthy aggression was associated with an increased likelihood of stroke incidence. The study additionally found that pathological levels of aggression were linked to hypertension, suggesting the contribution of hypertension to the association between aggression and stroke.<sup>39</sup> In contrast, one study reported that anger expression assessed by the Spielberger Anger-Out Expression Scale had a protective effect on stroke occurrence after following male professionals with a

high educational level for an average of 2 years. The relative stroke risk was 0.42 (95% CI, 0.20 to 0.88) when comparing the men with higher anger-out scores with those with lower scores.<sup>40</sup>

The discrepancy in the results might have been due to differences in the socioeconomic status (SES) or regional cultural/environmental factors. A recent meta-analysis found no significant association between anger and hostility and stroke risk.<sup>41</sup> However, after the exclusion of male professionals with high SES, anger significantly contributed to an increased stroke risk (hazard ratio, 1.30; 95% CI, 1.06 to 1.59). Thus, anger and hostility may be associated with stroke only in people with low SES. Additionally, the effect of anger may be influenced by urbanicity. A recent prospective study in Japan followed 5,936 residents of urban and rural communities (age range, 40 to 79 years) for an average of 16.6 years. The mean anger expression scores were similar between urban and rural residents, and 312 patients developed a stroke. Among urban residents, anger expression was positively associated with stroke risk (hazard ratio, 1.27; 95% CI, 1.05 to 1.54). In contrast, no association was found among rural residents (hazard ratio, 0.96; 95% CI, 0.85 to 1.09).<sup>42</sup> Although SES and urbanicity may be interrelated, previous studies have not examined this aspect. Therefore, further studies are required to examine whether SES and urbanicity are independent factors that modify the effects of anger.

### Anger as a triggering factor for stroke

Anger has been suggested as a triggering factor for stroke (Table 2). A hospital-based cross-sectional study in India assessed 11 potential trigger factors, including recent psychological stress, alcohol abuse, infection, drug abuse, sexual activity, and anger. Triggering factors were detected in 128 (44.2%) of the total 290 patients (46.4% had ischemic stroke and 36.4% had hemorrhagic stroke). Anger assessed <2 hours before stroke onset was identified in 12 (4.1%) patients.<sup>43</sup> Unfortunately, the result was difficult to interpret because of the lack of control participants.

Case-crossover studies can overcome this problem by adding more credibility to the study results. In these studies, patients with acute stroke were asked whether they were angry or emotionally upset immediately before the stroke symptom onset. Additionally, anger during the corresponding hours of the previous day was assessed. Although this method has limitations in that only alert and communicable patients can be enrolled, it has advantage because each individual can serve as his/her own comparator. Using this method, a study of 200 patients with acute stroke compared the anger intensity during a 2-hour hazard period prior to stroke onset with the intensity at

**Table 2.** Summary of the studies on anger as a risk /triggering factor for stroke

Study	Terminology	Stroke subtype	Age (yr)	Patient numbers (cases)	Follow-up	Tools	OR (95% CI)/Remarks	Covariates
<b>Anger as a risk factor</b>								
Everson et al. (1999) <sup>25</sup> Finland	Anger out/in/control	Incident stroke	53.0	2,074 (64)	8.3 yr	Spielberger Anger Expression Scales	2.03 (1.05–3.94) 6.87 (1.50–31.4)/history of IHD	Age, BMI, SBP, smoking, alcohol consumption, SES, HDL, LDL, fibrinogen, prevalent diabetes, use of antihypertensive medication
Williams et al. (2002) <sup>26</sup> USA	Trait anger	Incident stroke	48–67	13,851 (257)	6.4 yr	10-Item Spielberger Trait Anger Scale	2.82 (1.64–5.22)/≤60 years old 2.86 (1.56–5.25)/HDL >47	Sex, race/ethnicity Age, sex, race/ethnicity
Eng et al. (2003) <sup>40</sup> USA	Anger out	Incident stroke	61.9	23,522 (57)	2.0 yr	Spielberger Anger Out Expression Scales	0.42 (0.20–0.88)	Age, smoking history, alcohol intake, BMI, physical activity, hypertension, high serum cholesterol, diabetes, history of MI in parent aged less than 60, beta blocker use, antidepressant use, tranquilizer use, routine physical exam in last 2 years, energy-adjusted intakes of total fat, saturated fat, folate, and fiber, multivitamin and vitamin E supplement use, employment status, Berkman-Syme Social network Index
McCloskey et al. (2010) <sup>39</sup> USA	Unhealthy aggression (IED)	Stroke	35.7 (IED) 42.9 (control)	10,366 (204)		Collaborative Psychiatric Epidemiology Surveys (lifetime IED status)	2.01 (1.29–3.14)	Age, gender, race, marital status, education, smoking status, BMI, history of alcohol abuse or dependence, history of other drug abuse or dependence, previous accidents or injuries
Tezuka et al. (2020) <sup>42</sup> Japan	Anger in/out	CI, ICH, SAH, unclassified stroke	58.3 (urban) 56.9 (rural)	5,936 (204)	16.6 yr	Spielberger Anger In/Out Expression Scales	1.27 (1.05–1.54)/urban residents 0.96 (0.68–1.34)/rural residents	Age, sex, smoking, alcohol, BMI, hypertension, diabetes mellitus, hyperlipidemia
Tezuka et al. (2021) <sup>49</sup> Japan	Anger in/out	CI, ICH, SAH, unclassified stroke	59.4 (low PSS) 55.1 (high PSS)	1,806 (51)	18.8 yr	Spielberger Anger In/Out Expression Scales	1.43 (1.13–1.82)/low PSS 0.83 (0.49–1.40)/high PSS	Age, sex, smoking, alcohol, BMI, SBP, antihypertensive medication use, diabetes mellitus, hyperlipidemia
<b>Anger as a triggering factor</b>								
Koton et al. (2004) <sup>44</sup> Israel	Anger	CI, TIA	68.3	200 (200)	2-Hour hazard period, 2-hour control period	Onset Anger Scale	14.0 (2.8–253.6)	
Sharma et al. (2015) <sup>45</sup> India	Anger	CI, ICH, SAH	54.1	290 (290)		Onset Anger Scale	Anger (prevalence of 4.1%) is one of the triggering factors associated with higher NIHSS scores (CI), and higher hematoma volume (ICH, SAH)	
Smyth et al. (2022) <sup>45</sup> 32 countries including Canada	Anger, upset	CI, ICH, SAH	62.2	13,462 (13,462)	1 Hour before the onset of symptoms and during the corresponding 1 hour period on the previous day	A dichotomous question of 'Were you angry or emotionally upset?'	OR (99% CI) 1.37 (1.15–1.64)/all stroke 1.22 (1.00–1.49)/CI 2.05 (1.40–2.99)/ICH	

OR, odds ratio; CI, confidence interval; IHD, ischemic heart disease; BMI, body mass index; SBP, systolic blood pressure; SES, socioeconomic status; HDL, high density lipoprotein; LDL, low density lipoprotein; MI, myocardial infarction; IED, intermittent explosive disorder; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; PSS, perceived social support; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale.

the same period during the preceding day. The results showed an odds ratio (OR) of 14.0 (95% CI, 2.8 to 253.6).<sup>44</sup> INTER-STROKE investigators also conducted a case-control study involving 13,462 patients with first stroke from 32 countries. They adopted a case-crossover approach to determine whether a trigger within 1 hour of symptom onset (case period) versus the same time on the previous day (control period) was associated with acute stroke. A total of 1,233 (9.2%) patients were angry or emotionally upset during the case period. Anger or being emotionally upset in the case period was associated with increased odds of all stroke (OR, 1.37; 99% CI, 1.15 to 1.64), ischemic stroke (OR, 1.22; 99% CI, 1.00 to 1.49), and intracerebral hemorrhage (OR, 2.05; 99% CI, 1.40 to 2.99). No modifying effects of region, prior cardiovascular disease, risk factors, cardiovascular medications, time, or symptom onset day were detected.<sup>45</sup>

### Mechanisms

Several hypotheses have been proposed to explain the relationship between anger and stroke. First, an individual with an angry temperament may constantly have a high level of physiological activation, particularly sympathetic activation. This can lead to endothelial damage, increased vascular rigidity, and elevated blood pressure. A previous study reported that chronic anger suppression in men may increase hypertension risk, which predisposes individuals to develop cardiovascular disease.<sup>46</sup> Second, anger may result in increased cortisol release along with activation of the hypothalamo-hypophyseal axis. This may result in the disruption of vulnerable plaques, especially among patients with other risk factors.<sup>47</sup> Finally, anger may result in increased inflammatory and pro-thrombotic responses, thereby causing increased platelet aggregation and plasma viscosity and decreased fibrinolytic potential.<sup>48</sup>

### Possible interventions

As personality traits are difficult to change, the purpose of an intervention is not to change one's personality, but to encourage intervention efforts. As described above, a prospective cohort study showed that anger expression was associated with increased stroke risk among urban residents but not their rural counterparts.<sup>42</sup> Additionally, the authors reported that improving perceived social support mitigated stroke risk associated with anger.<sup>49</sup> These results suggest that living in less stressful conditions with proper social support may positively modify the effect of anger on stroke. However, further studies are required to obtain more substantial evidence for this strategy.

## Conclusions

PSA is prevalent during the acute and subacute stages of stroke. Thus, along with depression, PSA appears to be one of the main emotional symptoms observed in patients with stroke. PSA is associated with neurological deficits, depression, and emotional incontinence. Although the study results are heterogeneous, lesions involving the frontal-lenticular-brainstem pathway appear to be involved. Considering this, PSA seems to be (at least in part) related to neurochemical (e.g., serotonin) changes secondary to brain damage. However, patients' frustration associated with their functional deficits and hostile environments and genetic predisposition may also play a role in PSA development. Antidepressants, particularly SSRIs, are considered the management of choice. The recognition of PSA is important not only because it deteriorates patients' QOL and increases caregivers' burden, but also because it is treatable.

However, several limitations need to be addressed. First, a standardized method for diagnosing or measuring PSA severity has not yet been established. Second, in most PSA studies, patients with severe aphasia or cognitive impairment were excluded. Thus, PSA prevalence is probably underestimated. Third, data from different continents (e.g., Europe, North America, and Asia) may generate further confounders because of the differences in the healthcare system across countries. Finally, studies involving large patient populations, appropriate controls, and well-designed clinical trials are rare. Thus, further research considering these limitations is needed to improve the understanding and management of PSA.

Here, we have discussed that studies have shown that anger is a risk or triggering factor for stroke. However, it remains unclear whether the negative effects of anger are independent from the modification of known risk factors, including hypertension. There have been suggestions that the negative effect of anger may be modified by patients' social status and environment. Therefore, more research is needed to clarify the role of anger as a risk factor for stroke and to develop strategies to prevent stroke by appropriately managing anger.

## Disclosure

The authors have no financial conflicts of interest.

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