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Detection to Hospital Door: Gender Differences of Patients With Acute Stroke Symptoms

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Although prehospital stroke management is challenging, it is a crucial part of the acute stroke chain to enable equal access to highly specialised stroke care. It involves a critical understanding of players usually not specialized in acute stroke treatments. There is contradictory information about gender inequity in prehospital stroke detection, dispatch, and delivery to hospital stroke centers. The aim of this narrative review is to summarize the knowledge of gender differences in the first three stages of acute stroke management. Information on the detection of acute stroke symptoms by patients, their relatives, and bystanders is discussed. Women seem to have a better overall knowledge about stroke, although general understanding needs to be improved. However, older age and different social situations of women could be identified as reasons for reduced and delayed help-seeking. Dispatch and delivery lie within the responsibility of the emergency medical service. Differences in clinical presentation with symptoms mainly affecting general conditions could be identified as a crucial challenge leading to gender inequity in these stages. Improvement of stroke education has to be applied to tackle this unequal management. However, specifically designed projects and analyses are needed to understand more details of sex differences in prehospital stroke management, which is a necessary first step for the potential development of substantially improving strategies.

Keywords: prehospital, acute stroke, management, women, gender inequity

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INTRODUCTION

Acute stroke care and access to timely treatment strongly depend on efficiently organized prehospital management. The stroke chain of survival with its first 3 “Ds”, detection, dispatch, and delivery, based in the prehospital setting emphasizes the importance of optimal pathways before the patients arrive at the hospital (1). There is contradictory information about gender inequity in acute stroke treatment. A German nationwide cohort analysis with >1 million patients identified a higher probability of men receiving stroke unit treatment (OR, 1.11; 95% CI, 1.09–1.12) with a lower in-hospital mortality (OR, 0.91; 95% CI, 0.89–0.93) compared to women (2). However, intravenous thrombolysis (IVT) treatment numbers were similar in this study and more women received endovascular treatment (EVT). A Swedish analysis confirmed significantly lower numbers of women receiving stroke unit care in their cohort (3). In contrast, a retrospective analysis of

patients with acute ischemic stroke (AIS) arriving at hospital within 2 h after symptom onset from the American Get-With-The-Guidelines-Stroke registry identified female sex as a risk factor for not receiving IVT (4). It is unclear whether these differences are caused by an already existing gender inequity in the very first prehospital stages of acute stroke care in different regions. This review gives insights into available knowledge on gender differences from symptom onset until arrival at the hospital emergency department and discusses available information on detection, dispatch, and delivery of the acute stroke management cascade.

DETECTION OF ACUTE STROKE SYMPTOMS

Identification of acute symptoms of stroke can be challenging even for specialists. However, this is the first crucial step in gaining access to modern stroke treatment, especially to recanalizing therapies with a time-limited treatment window for the best outcome. Most of the current literature describes a better recognition and identification of acute stroke symptoms by women, but there are also publications emphasizing their lack of stroke understanding.

Differences in Stroke Knowledge

A meta-analysis of 22 studies, of which 20 were cross-sectional and 2 pretest–posttest design surveys, mainly conducted in the USA and Canada, identified a greater knowledge of stroke symptoms and related risk factors in women compared to men (5). In a Spanish randomized study, in which knowledge about stroke symptoms and risk factors was collected with structured face-to-face questionnaires, no sex difference could be detected in general knowledge about stroke, but women showed a higher understanding of risk factors. However, they were less likely to call an ambulance (6). In contrast, in a cross-sectional Chinese study, in which men and women with stroke and hypertension were questioned regarding their stroke knowledge and behavior, men demonstrated a better knowledge about stroke but had a worse pre-stroke health behavior than women (7). An American stroke survey performed with a limited number of stroke survivors detected women as significantly more likely compared to men to identify all the five traditional warning signs of stroke and subsequently take the correct action by calling the Emergency Medical Service [EMS; (8)]. In 4 Canadian cross-sectional surveys, in which public awareness campaigns including information about stroke preceded a stroke-knowledge questionnaire about face, arm, speech symptoms, a clear association of limited knowledge with male sex was found [Odds ratio 0.68; 95% CI: 0.53, 0.86; (9)].

In addition, the overall perception of stroke knowledge in women is poor. A survey of 1,024 women contacted by randomly selected telephone numbers in the USA in 2003 identified that only one-fourth of all women felt well informed about stroke and stroke risk and just below a quarter reported to be very concerned about the disease. Standing out was that younger women aged 25–34 years had the highest rate of nescience (37%). Hispanic or

Black ethnicity was associated with less knowledge, but correct identification of acute stroke symptoms was low for all age groups and independent of racial backgrounds (10).

The above examples of available evidence (summarized in **Table 1**) emphasize that in many countries women are not generally underprivileged in their knowledge about stroke and understanding of the necessary actions to take. But, knowledge in general still needs improvement and differs not only between the countries but also between different ethnic groups. Both latter stress the need for tailored regional educational programmes involving women of all ethnic groups. A one-fit-all approach will not reach the aim.

Another possibility to increase stroke knowledge is to address pupils rather than only adults and to integrate medical education into school programmes. There is only limited information about the potential benefits of an early school education about stroke and stroke symptoms. However, there seems to be no gender difference. In an 11-question multiple-choice stroke awareness survey with >600 American High school pupils, no difference in stroke symptom knowledge between girls and boys was detected (14). A randomized controlled, multiethnic school-based intervention study called “Kids Identifying and Defeating Stroke” (KIDS), which was started in middle schools enrolling 8,827 pupils in Texas, USA investigated whether a structured stroke education campaign for their year 6 to year 8 pupils could improve stroke knowledge and necessary emergency actions. The programme was performed as four 1-h classes each year, taught by health teachers and neurologists, and included a homework assignment involving parents. A significant increase in stroke knowledge and correct reaction to witnessed symptoms of students’ in the KIDS group compared with controls could be observed. The result did not show any gender differences (12). No information could be found from other countries. Also, it stays unclear whether school educational programmes can lead to a longer-lasting increase in the overall understanding of stroke symptoms, and emergency actions needed. This requires further investigation.

Educational Effect of Public Awareness Campaigns

Public awareness campaigns, comparable to advertisements promoting products or services, are general means that use mass media and new media to transfer information.

It is very well described that most public awareness campaigns can improve stroke knowledge only for a short amount of time, usually lasting between 3 and 6 months (25). Interestingly, it seems that there is a gender difference in susceptibility to such campaigns. A randomized study analyzing the effect of a posted information letter about stroke symptoms showed that the outcome of reduction of prehospital times was only significant for women (13). This could be explained by the finding from a cohort analysis in the Czech Republic, where a sample of 1,004 people were interrogated about their stroke knowledge. Women showed significantly higher interest in the information than men (11). Nevertheless, it stays unclear whether permanently repeated public awareness campaigns in the spirit of “Groundhog Day”

TABLE 1 | Studies addressing gender in prehospital stroke management.

Reference	Location	Study design	Participants n	Results for women
Detection				
Bártlová et al. (11)	Czech Republic	Cohort study	1,004	Women show more interest in stroke information
Ferris et al. (10)	USA	Telephone survey with randomly selected women	1,024	Only 25% women feel well informed
Focht et al. (8)	USA	Cohort survey	71	Women know more stroke signs and more likely to take correct actions
Li et al. (7)	China	Cross-sectional survey	272 men and 118 women	Women less knowledge about men, but better pre-stroke health behavior
Morgenstern et al. (12)	USA	RCT	573	Girls and boys show equal knowledge after stroke education
Mueller-Nordhorn et al. (13)	Germany	RCT	75,720	Women show reduced prehospital times after posted stroke information
Ramírez-Moreno et al. (6)	Spain	RCT	2,409	Women show higher understanding of risk factors, but EMS alerted less often, no difference in general stroke knowledge
Rioux et al. (9)	Canada	Cross-sectional survey	2,451	Women show better knowledge after awareness campaign
Stroebe et al. (5)	USA, Canada	Metaanalysis	20 cross-sectional, 2 pre-posttest surveys	Women show greater knowledge about stroke and risk factors
Umar et al. (14)	USA	Cohort survey	608	No difference in stroke knowledge of girls and boys
Dispatch				
Barr et al. (15)	Australia	Cohort study	150	Fewer women recognized the importance of immediate transfer to hospital
Buck et al. (16)	USA	Cohort study	871	More women than men were misidentified by EMS dispatcher
Mainz et al. (17)	Denmark	Cohort study	5,356	Women living alone have longer total prehospital time delay
Mochari-Greenberger et al. (18)	USA	GWTG registry	398,798	Hispanic, Asian, Black women less likely to use the EMS
Springer and Labovitz (19)	USA	Cohort study	1,940	Women more often found down, leads to admission delay
Delivery				
Govindarajan et al. (20)	USA	Registry cohort	3,787	Fewer women are correctly diagnosed by EMS
Hsieh et al. (51)	Taiwan	Cohort study	928	More men are pre-notified to hospital
Leung et al. (21)	Hong-Kong	Cohort study	298	More men are pre-notified to hospital, pre-notification associated with shorter treatment times
Lin et al. (22)	USA	GWTG registry	371,998	Fewer women are transferred with pre-notification
Madsen et al. (23)	USA	Cohort study	1,991	Females living alone are at higher risk to have delayed hospital arrival compared to men
Mould-Millman et al. (24)	USA	Cohort study	548	Women have lower sensitivity to be correctly diagnosed at the emergency site

could lead to a more solid understanding of stroke of all genders and ethnicities.

DISPATCH: INVOLVEMENT OF EMS

Early activation and dispatch of EMS is a vital element in the acute stroke chain of survival (26). The use of EMS is associated with shorter times to treatment (27); however the

existing literature evidences a large degree of variation in how quickly patients alert the EMS and the subsequent dispatch of a medical resource. Prehospital delays can range from 20 min to >150 h based on a number of factors, including the patient's awareness of the severity of their symptoms with data suggesting that female patients with stroke experience an increased delay time in calling for help (15).

There is a paucity of contemporary evidence surrounding sex differences in activation and dispatch of EMS; however there is

a recognized inequity in emergency care access in women with stroke, which may be a result of delay in EMS dispatch (28). In a study of 5,515 patients with stroke in the Netherlands, symptom onset to door time was found to be on average 27 min longer in women than in men (29). This finding can be caused by multiple different underlying reasons, of which some are discussed below and are summarized in **Table 1**.

Willingness to Call

Existing literature presents an inconsistent picture of sex differences in the activation of EMS. Ramirez-Moreno et al. (6) studied responses from 2,409 participants aged 18 and over, who were surveyed through face-to-face interviews consisting of open-ended questions about the respondent's hypothetical answer to presenting or witnessing signs of a stroke and upon suspecting stroke or transient ischemic attack (TIA) in a family member or themselves. An appropriate response to a suspected stroke was indicated by 83.4% of men compared to only 77.5% of women. These findings are corroborated by further research which suggest that women are more likely to delay accessing emergency care than men, with some literature suggesting that the odds of being admitted to hospital within 3 h of symptom onset was 10% lower for women than men (30). Possible reasons for the disparity in the response to stroke symptoms between men and women may include a difference in perceived severity of the symptoms with women underestimating the urgency of the situation (6). But there are also intrasexual differences. Data analyzed from 398,798 American Get-with-the-guideline stroke registry patients, identified Hispanic or Asian or Black women compared to White women as less likely to use the EMS when stroke symptoms occurred [aOR, 95%CI: Black: 0.87, 0.84–0.91; Hispanic: 0.71, 0.67–0.74; Asian: 0.71, 0.67–0.76; (18)].

Reasons for Delayed Calling

Delayed calling for help might have multiple underlying causes. An American questionnaire study assessing attitudes toward response to stroke onset found that women, who arrived at hospital over 3 h after symptom onset, cited reasons such as not wanting to trouble others, opting to see if their symptoms might resolve, hiding their symptoms from others, and trying to continue with their normal activities for a delay in seeking emergency care (31). This finding demonstrates some plausible reasons for the delay in EMS dispatch, and therefore hospital arrival, that impacts the eligibility for recanalizing treatments due to arriving outside the treatment window (17).

Whilst the study did not include men and therefore provides no opportunity for comparison with regard to responses, it is recognized that there are sex-specific differences in the way in which medical assistance is summoned following the onset of stroke symptoms, which can result in a delay in dispatch for women (32). In a study of 150 patients with stroke in Australia, it was found that women experienced a delay in symptom onset to presentation to ED that was a mean average of 1.4 h longer than men, with knowledge and recognition of stroke symptoms and not recognizing the importance of their symptoms significantly impacting this delay (15).

Impact of Difference in Social Situations

If a stroke is witnessed, the activation of EMS is substantially shorter than if symptom onset was unwitnessed (33). It is, therefore, reasonable to suggest that living alone may result in a higher incidence of stroke with an unwitnessed symptom onset and therefore delayed EMS dispatch. Mainz and collaborators published in 2020 (17) the higher proportion of women living alone at the time of their stroke as a likely cause for a longer delay in symptom onset to EMS call. Their study found that this “patient-dependent delay” for women was 19.8 min longer than for men, with living alone being associated with a longer total prehospital time delay. About 50.4% of women lived alone compared to only 31.7% of men.

A retrospective cohort analysis of 1,904 hospital patients with stroke in New York, USA identified that women are significantly more often found with severe stroke symptoms unable to seek help on their own (“found down”) and that this led to all of them arriving 3 h or later after onset (19).

If the onset of stroke symptoms is witnessed, it is most commonly by the patient's partner (34); however more women than men are widowed at the time of stroke and therefore live alone, with a delay in EMS dispatch a plausible consequence of this (35). The caller was the patient themselves in only 3% of cases based on a study of 198 patients transported to the emergency department (ED) by EMS in Melbourne (34), further supporting the hypothesis that women are susceptible to delays in EMS dispatch.

Another reason adding to the gender difference in EMS activation might be that women are older than men at the time of stroke, particularly in Europe, Australia, and South America (36). This results in a higher level of functional limitation prior to their stroke (35, 37), which may impact their physical ability to summon help.

Role of the Emergency Medical Service Dispatch Center

The identification of stroke symptoms at the point of EMS dispatch is key in optimizing the chain of survival in acute stroke and this remains one of the least investigated elements of the chain (38). It is critical that dispatch centers accurately identify stroke to avoid the assignment of an incorrect “code” and cause subsequent delays in EMS dispatch (39). There are many differences in the organization of EMS worldwide (40); however findings show a stark variation in the proportion of strokes correctly identified at the point of dispatch with successful identification ranging from 45 to 83% (16, 41).

In some countries, the Medical Priority Dispatch System (MPDS) is used for EMS dispatch. This system is based on a structured caller interrogation with additional instructions on what to do until EMS arrival. In a Los Angeles study of 871 patients, 58 were assigned the stroke MPDS code by the dispatcher, but only 45% received a confirmed in-hospital stroke diagnosis (16). A total of 56.2% of female patients with stroke were misidentified in this study. In a review of existing literature, Oostema and collaborators (42) found that despite the use of a stroke screening tool, the recognition of stroke

by the dispatch center was inadequate and it is suggested that many subtle stroke presentations may be misidentified (39). A barrier to the identification of stroke symptoms at the point of dispatch is the variety of presenting symptoms that may fall outside of the screening system adopted by the communication center. With women more likely to experience non-traditional stroke symptoms, an inherent risk not only of incorrect call coding at the point of dispatch with subsequent delays in timely EMS care but also of EMS identification of a woman with stroke, decelerating the delivery to the stroke center, has to be considered.

DELIVERY TO HOSPITAL

There are many reports on differences in clinical presentation between men and women [Table 1; (43)]. This likely not only affects stroke patient's identification at the dispatch center level but also at the scene, influencing the delivery step of the acute stroke chain of survival. Delivery comprises of rapid EMS identification of stroke symptoms, management of the patient on the scene, and timely transportation and prenotification to the hospital, as defined by the American Heart Association (44).

Gender Differences in Stroke Presentation and EMS Recognition

Women are reported to often present with unusual stroke symptoms such as generalized weakness, fatigue, and mental status change. In an analysis of 461 patients, 52% of women compared to 44% of men presented with a non-traditional stroke symptom (43). This result was primarily driven by the number of women with mental status changes, a symptom caused by many other differential diagnoses (45). Further studies confirmed that non-traditional stroke symptoms were present in 51.8% of women compared to 43.9% of men (46). In addition, disorientation, visual disturbance, dizziness headache, general pain, urinary incontinence, or changes in consciousness are specifically described to be shown in female stroke (47, 48).

These reported differences in the clinical presentation of stroke between genders can therefore be of challenge for the EMS when diagnosing stroke in the prehospital environment with only limited diagnostic tools available. This is supported by multiple studies (49). A recent systematic meta-analysis of 21 observational studies with 6,934 stroke and transient ischemic attack patients identified that 26% of all patients with stroke, who were missed by the EMS, presented with non-FAST symptoms like speech abnormalities, nausea/vomiting, dizziness, changes in mental status, and visual disturbance (41). A study with 3,787 patients transported by EMS found that only 30% of women compared to 35% of men received a correct diagnosis of stroke, with these findings perceived to be based on the non-traditional stroke symptoms displayed more frequently by women (20).

Various measures have been previously discussed to enhance prehospital stroke recognition, including the use of validated stroke scales (50). A retrospective analysis of 548 emergency patients in Atlanta, USA evaluated that paramedics were more likely to positively identify stroke when the Cincinnati Prehospital Stroke Scale (CPSS) was positive. However,

sensitivity to be diagnosed at the scene was lower for women than men [odds ratio 0.53, 95%CI 0.17–1.63; (24)].

It is likely that different presentations of women with acute stroke lead to a wrong working diagnosis by the EMS in the prehospital phase, which could impact further stroke management. However, more prospective studies are needed to understand the real impact.

Gender Differences in EMS On-Scene Time Metrics and Prenotification to Hospital

A large study of nearly 2,000 patients presenting with AIS found that before adjustment, the time of symptom onset to arrival at the hospital *via* the EMS was slightly longer in women (mean 337 min vs. 297 min in men); however, they subsequently found that gender was not associated with a delayed time to arrival when considering age and National Institute Of Health Stroke Severity (NIHSS) score. It was demonstrated that 30% of women in the study (324/1097) lived alone compared to 22% of men (200/894), and that this was a factor in delayed arrival at the hospital, potentially due to the lack of self-recognition of symptoms (23). A study of 5,356 patients identified that 40.5% of women and 44.4% of men arrived at the stroke unit within 3 h of symptom onset, and similarly living alone was deemed to be a contributory factor involved in this finding. About 54.4% (1,256) of women were documented as living alone, leading to an average delay of 20 min longer than their male counterparts (17).

A study from 2016 demonstrated an association not only between pre-notification and faster door to computed tomography (CT) scan in patients presenting within 3 h of symptom onset but also a shorter door-to-needle (DTN) time. This study comprised of 928 patients, of whom 727 received pre-notification to the hospital. There was a significantly higher number of men who were transported with pre-notification (64.5%), and more pre-notified patients had a DTN of < 60 min (45.1 vs. 28%) compared to those not pre-notified (51). A similar pattern was shown in a study from Hong Kong, which found that the ratio of men to women receiving pre-notification to hospital for stroke was 1.22:1. Pre-notification was also demonstrated to improve door-to-CT and DTN time (21).

An analysis of the American Get-with-the-Guideline stroke registry of 371,998 enrolled patients with stroke in 1,585 hospitals over 8 years showed a pre-notification rate of 67%. Patients with EMS pre-notification to the hospital were more likely to be younger, white, and male. In the 122,791 patients eligible for pre-notification where none was given, 54.3% were women (22).

These differences in prehospital management of women with acute stroke might be caused by a higher number of misdiagnoses, subsequently leading to lower numbers with accurately initiated stroke alert to the hospital. But clearly, further research is required to understand unbiased differences in prehospital treatment and outcomes.

DISCUSSION

This review addresses gender differences in the very first stages of acute stroke management, the detection of disease symptoms to the delivery of the suspected stroke patient to the specialized

center. It highlights some of the available evidence with the aim to raise awareness and identify a pattern, hinting toward areas of necessary improvement to guarantee gender equity in prehospital acute stroke treatment.

Detection of acute stroke and initiation of the necessary steps, which enable health care specialists to administer up-to-date and high-quality stroke care, is incumbent to the patient and/or relatives or bystanders. There is a lot of evidence coming from different countries that women have a better knowledge about acute stroke symptoms, risk factors, and the necessary actions to take than men. However, the overall public level of knowledge about stroke, the number three disease cause for disability is still poor (52, 53). Gender inequity in the detection of stroke seems to show geographical differences, but further systematic evaluations are needed to understand where and what differences exist.

Despite often having a higher and better knowledge about stroke, women seem to feel uncertain about many aspects of the disease. Women's confidence in their own knowledge differs from that of men (54), which needs to be considered and addressed in educational programmes.

The idea to implement health education in standard school programmes would be one possibility to establish gender-independent knowledge transfer in the future. But, to reach girls and young women in countries with relevant sex inequity would need strong collaboration between health services and educational sectors with strong political and governmental support.

It is well described that public campaigns do not lead to a sustainable solution to improve health awareness (1); however it seems that women are more likely and willing to pick up information provided by mass media campaigns (55).

However, equal knowledge and awareness alone do not lead to equal acute stroke care. The available evidence suggests that women arrive at the hospital later than men, indicating an inequity in dispatch and delivery of acute stroke care. Relevant confounders like social disparity with more women living alone at an older age, when the risk of stroke increases, have to be considered. Management of women seeking help at an emergency

medical dispatch center does not seem to show any gender-based differences. But many countries use systematized interrogation programmes, like the Medical Priority Dispatch System to identify stroke suspects, which could be prone to errors and disadvantageous to women with stroke, who often present with non-traditional symptoms (43).

There is no information available on whether a criteria-based dispatch, used in many Nordic and European countries (56), which relies on the experience of the telecommunicator, is less prone to misidentify women with suspected strokes. More studies comparing both modes of emergency service dispatch are needed to identify gender-related challenges of different dispatch systems.

The differences in the clinical presentation of women compared to men can make it difficult for paramedics to quickly conclude a stroke working diagnosis at the emergency site. This likely presents the biggest challenge in the delivery of equal care. There is evidence for an inequity in pre-notification of cases to the receiving hospital. To tackle this, paramedic and EMS stroke-specific training have to be considered and addressed. A correlation between high-quality medical education and patient outcome has been demonstrated for nurse care (57, 58), but data for the EMS or, more important, training programme adjustment for prehospital staff is lacking.

To conclude, more structured data and results from specifically designed clinical trials are needed to understand gender inequity in the first stages of acute stroke care and to develop solutions to overcome potential gender imbalances. Identified gender inequity is mostly caused by unawareness of gender-specific aspects of stroke, which are not considered in acute prehospital pathways.

AUTHOR CONTRIBUTIONS

SW, BW, RM, and KF contributed to the conception and design of the review. SW, BW, and RM wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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