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NEUROLOGICAL UPDATE

Revisiting 'progressive stroke': incidence, predictors, pathophysiology, and management of unexplained early neurological deterioration following acute ischemic stroke

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Abstract Early neurological deterioration (END) following acute ischemic stroke is a serious clinical event strongly associated with poor outcome. Regarding specifically END occurring within 24 h following stroke onset, apart from straightforward causes such as symptomatic intracranial haemorrhage and malignant edema, the cause of END remains unclear in more than a half of cases. In the latter situation, patients are often referred to as 'progressive stroke', a default clinical category that does not imply underlying mechanisms, precluding informed management. In this review article, we summarize the available evidence on the incidence, predictors, and associated factors of unexplained END, and discuss its underlying pathophysiology. We particularly address the hemodynamic and thrombotic mechanisms that likely play a critical role in unexplained END, and in turn highlight potential new avenues to prevent and manage this ominous event.

Keywords Acute stroke · Deterioration · Thrombolysis · Penumbra · Cerebral ischemia

Introduction

Following the licensing of intravenous recombinant tissue-type plasminogen activator (r-tPA), the management of acute ischemic stroke (AIS) has shifted towards the hyperacute stage. Currently, all patients with AIS should be admitted to stroke units as soon as possible for urgent neuroimaging, implementation of revascularization therapy (i.e., r-tPA and/or mechanical thrombectomy—MT) if indicated, and prevention and monitoring of early recurrence and medical complications. However, despite these major improvements, the clinical course in the first 24 h remains largely unpredictable [1], underlying the need to better investigate this time period. Although the majority of patients with AIS significantly improve within this time frame largely thanks to salvage of the ischemic penumbra, a sizeable fraction does not recover or even deteriorate, so-called 'early neurological deterioration' (END). Because END consistently predicts poor outcome [2], it is of considerable importance to prevent and, if applicable, treat this ominous event. However, END is a clinical situation with widely different causes [3], and efficient prevention and management of END will obviously depend on the underlying cause. As will be seen in the following, although the underlying mechanism/cause is straightforward in a good fraction of ENDs, it is less clear in the majority.

Symptomatic intracranial haemorrhage (sICH) and malignant edema are the two main straightforward causes of END. Their mechanisms and predictors have been extensively investigated, leading to specific management according to published—though not always standardised—guidelines [4]. Additional straightforward but unusual causes include early seizures, early recurrent ischemic stroke in a different arterial territory (ERIS), and early systemic medical complications (e.g., massive myocardial infarction and pneumonia) [2, 3]. However, over half of all ENDs have no clear cause and are often referred to as 'progressive stroke' [2, 3, 5], a default clinical category that is descriptive and does not imply a specific mechanism. However, despite a growing literature on END in the

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three last decades, the mechanisms underlying this particular and major END subtype remain poorly understood. Accordingly, no guidelines are available for this situation, and hence, no clear action is usually taken to prevent or reverse the deterioration and prevent poor outcomes. To highlight the fact that the mechanism(s) underlying 'progressive stroke' are unclear and that research is required to address them, we have recently renamed this entity 'unexplained END' [6–8], and will use this operational terminology in the following.

In this review article, we will summarize the available data on the incidence and mechanisms of END in AIS patients who are candidates for revascularization therapy—i.e., mainly large vessel strokes reaching hospital within 8 h of stroke onset, with a strong emphasis on unexplained END. Given that END occurring >24 h following this category of AIS patients generally has a definite and straightforward cause [5, 9], the present review will focus on END occurring within the first 24 h. After addressing the definition, incidence, and causes of END, we will review the literature regarding more specifically the predictors, associated factors and pathophysiology of unexplained END, with a final note on management avenues.

Definition of END

Many definitions of END have been used so far, depending on the stroke scale used to assess deterioration, degree of worsening, and time frame of the deterioration [2, 10]. An appropriate definition should allow END to be detected as a functionally meaningful change in neurological status at the bedside, in an easy and reliable fashion. Thus, an increase in the National Institutes of Health Stroke Scale (NIHSS) score of ≥4 points (out of a total score of 42) between admission and 24 h (ΔNIHSS ≥ 4) has been used in most studies so far [2], particularly in recent publications, because it seems clinically relevant and because the NIHSS is the most widely used neurological scale in the acute stroke setting. However, some limitations of this scale and the above cutoff need to be mentioned for the clinical relevance of END assessment. First, although the intra-rater and inter-rater reliability for individual NIHSS items is good, the overall score may have more substantial variability [11]. Therefore, a small change in total NIHSS score (e.g., ΔNIHSS = 2) might reflect inadequate reliability rather than true END, notably with high scores (i.e., severe stroke). Therefore, using the latter cutoff, true END might get mixed up with a stable course, whose underlying pathophysiology and implications are likely different. Second, the NIHSS is highly skewed in functional significance, and <4 points deterioration could still be functionally meaningful, for example, in the context of minor stroke [10, 12]. Thus, using relative or normalised instead of absolute deterioration scores, such as percentage change from admission NIHSS, might have increased clinical relevance [1]. Accordingly, END would then be considered as a larger score increase for high than for low baseline NIHSS scores. However, these approaches have their own limitations, including poor bedside practicality.

In our view [2], future studies should use the ΔNIHSS ≥ 4 definition to study true END patients as well as for harmonization, whereas a lower cutoff (e.g., ΔNIHSS ≥ 2) could be used in specific studies on minor strokes, where even small deteriorations have clinical significance. Nevertheless, the following review will focus on the literature reporting END occurring within 24 h based on no specific cutoff.

Incidence and causes of END ≤ 24 h

Incidence of all-cause END in the absence of revascularization therapy

Two studies from the pre-thrombolysis era assessed the incidence of END using the ΔNIHSS ≥ 4 criterion, reporting figures of 16.3 and 17.6%, respectively [13, 14]. With respect to the post-thrombolysis era, very little data on END in non-thrombolyzed patients are available, as most AIS patients with non-mild symptoms reaching hospital within the early time window receive revascularization therapy. Two recent studies reported the incidence of END in non-thrombolyzed minor strokes (defined as admission NIHSS ≤ 5) with proximal arterial occlusion [15, 16], a category of patients where revascularization therapy is a matter of current debate. The reported incidence, defined as a worsening of NIHSS ≥ 1 in one study [15] and NIHSS ≥ 2 in the other [16], was 23 and 41%, respectively. This worryingly high END rate in non-thrombolyzed minor strokes with proximal occlusion is consistent with two similar recent studies on END occurring within 48 h [17] and 5 days [18] of admission, respectively.

Incidence of all-cause END in AIS patients treated with revascularization therapy

In a recent systematic review [2], a meta-analysis showed an average incidence of END following r-tPA and using the ΔNIHSS ≥ 4 definition of 13.8% (CI95%: 10.0–17.7%). This figure was recently largely confirmed in a study including more than 300 r-tPA patients [6] and in another smaller study [19] (11 and 10%, respectively). A study based on a large cohort recently reported a lower incidence (6%), which might, however, be explained by differences in stroke populations studied [20].

We found no published data on END ≤ 24 h following MT, probably because this therapy has only recently been adopted. None of the recent randomized control trials (RCT) comparing MT vs. best medical treatment in AIS with proximal occlusion reported rates of END occurring within the first 24 h, save for sICH, which was similar in both groups (average: 4.4 vs. 4.3%, respectively) [21]. One observational study reported an END rate of 9% following MT for M2 occlusions; however, the time frame for END was not mentioned [22].

Causes of END

In *non-thrombolyzed* patients, sICH was as expected found to represent a small fraction (<7%) of all ENDs [2]. No data on other potential causes for END are available in this clinical context, and therefore, no direct estimate of incidence of unexplained END is available. It is, however, likely that the vast majority of ENDs following untreated minor stroke is not due to sICH or malignant infarction. Hence, minor stroke would entail a high incidence of unexplained END, in turn accounting for the current debates regarding management of this entity [23].

In thrombolyzed patients, our recent systematic review revealed that the cause of END following r-tPA was also rarely specified, except for sICH which represented ~20% of all ENDs [2], a figure confirmed in further studies [5, 6, 20]. Although data were scarce at the time of this systematic review, malignant edema was estimated to account for at most 1/4 of all ENDs [2]. This was recently confirmed in two studies reporting rates of 6 and 12% using the ΔNIHSS ≥ 4 definition [6, 20], while another study using the ΔNIHSS ≥ 2 definition reported a rate of 26% [5, 6, 20]. Importantly, however, this complication tends to develop beyond the first 24 h [24], so that malignant edema may represent a higher fraction of ENDs covering longer time frames. Other causes, such as ERIS, seizures and other medical complications, seem in fact anecdotal [2, 6, 20, 25, 26]. Based on the above estimates of END causes, therefore, over half of all ENDs occurring after r-tPA would have no immediately identifiable mechanism. This estimate was recently confirmed in a large study reporting that 70% of all ENDs following r-tPA alone had no clear cause [6], and in two additional large-scale studies mixing patients treated with r-tPA alone and r-tPA followed by endovascular treatment, reporting figures of 47% [5] and ~70% [20]. However, differences in the absolute rate of END between the Seners et al. [6] and Simonsen et al. [20] studies are probably a reflection of different stroke populations (a fraction of the patients underwent bridging therapy in Simonsen et al.), and as such the absolute incidence of unexplained END (using the ΔNIHSS ≥ 4 definition) in the two studies differed markedly, at 7 and 4%, respectively. In the third study [5], the incidence was 13%, but the ΔNIHSS cutoff used was ≥2. Importantly, two of these studies found that low NIHSS was a significant predictor of unexplained END [5, 6].

The distribution of END causes following MT has not been reported so far, and will need to be studied in the future.

Predictors, associated factors, and pathophysiology of unexplained END ≤ 24 h

We will now discuss the predictors, associated factors, and pathophysiology of unexplained END. Readers seeking information on sICH and malignant edema are referred to published comprehensive reviews [27–30]. In addition, END following lacunar stroke, a clearly separate entity with likely different mechanisms [31], is beyond the scope of this review and will not be discussed here.

Extension of symptomatic ischemic tissue into asymptomatic tissue

Although 'progressive stroke' has long been thought to be of 'ischemic origin', no formal pathophysiological hypothesis based on the classic 'core-penumbra' model [32] was proposed, not to mention actual data at the tissue and vascular level. Thanks to its operational definition, the concept of unexplained END [6–8] has allowed one to formulate clear hypotheses and to formally test them in appropriately selected patient cohorts.

One influential hypothesis to account for unexplained END is extension of 'symptomatic' ischemic tissue (i.e., core and/or penumbra) into the surrounding 'asymptomatic' tissue (i.e., benign oligemia or non-hypoperfused tissue), as a result of secondary hemodynamic and/or metabolic events affecting the latter [33]. To test this hypothesis, our group assessed whether, and if so how far, the initial diffusion-weighted imaging (DWI) lesion grew beyond the acute penumbral zone (defined using admission perfusion imaging) on the 24-h follow-up MRI, using a sample of 10 unexplained END patients with a complete imaging dataset, compared to 30 matched no-END controls [7]. This exploratory study supported the above hypothesis, as infarct growth beyond the initial penumbra was indeed significantly larger in unexplained END patients than controls, and occurred in 9 of 10 END patients (substantial in 8) [7]. In addition, supporting our findings, the NIHSS increment was proportional to the volume of extra-penumbral lesion growth, and the topography of the latter roughly matched the NIH items that deteriorated [7]. Figure 1 provides an example of infarct growth beyond the initial penumbra in one patient with unexplained END following r-tPA. Unexpected infarction of acutely asymptomatic (i.e., non-core non-penumbral) tissue had been reported in an earlier study, involving substantial volumes

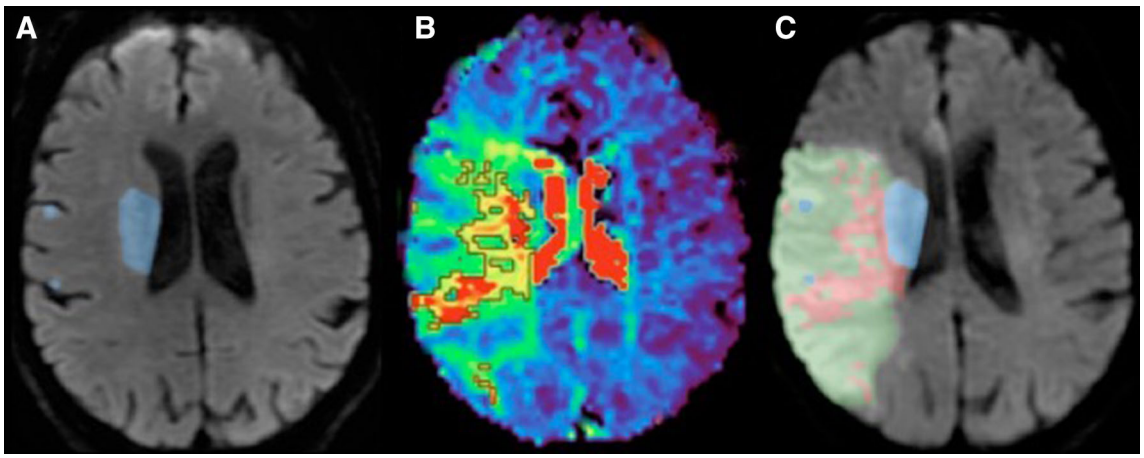

Fig. 1 Illustration of extension of symptomatic ischemic tissue into asymptomatic tissue in a patient with unexplained END. A 84-year-old patient presented with proximal right MCA occlusion. Her initial NIHSS was 14. She was treated with r-tPA only. **a** Pre-treatment DWI imaging showing a small initial core (*blue area*). **b** Pre-treatment PWI sequence (T_{max} map) showed a larger area of severely hypoperfused tissue ($T_{max} \geq 6$ s, area surrounded) and an extensive area of mildly hypoperfused tissue. Neurological deterioration occurred 2-h post-r-tPA, with a worsening facial palsy and left leg sensorimotor deficit (NIHSS 18), with no haemorrhage or oedema on CT. The 24-h follow-up MRI showed both intra- and extra-penumbral extension of the DWI lesion (*red and green*, respectively), the latter involving the primary sensorimotor cortex (**c**)

in ~10% of patients and associated with reduced 1-month clinical recovery [34]. However, the timing of this event could not be assessed as follow-up structural imaging was performed at the 1-month timepoint, while the relationship to END was not presented. In line with the above findings, two recent studies also pointed to the occurrence of 'new DWI lesions' at day 7 post stroke, involving areas initially affected by only mild (non-penumbral) hypoperfusion or 'outside the area of hypoperfusion' [35, 36]. However, whether END was associated with these radiological observations was again not reported.

The next key question is: What are the mechanisms that allow for the initially asymptomatic tissue to become recruited into the infarct, and hence cause END? Various secondary processes worsening neuronal status and/or perfusion in asymptomatic tissue have been proposed, namely, tissue events directly affecting neuronal survival, e.g., hyper/hypoglycaemia, and vascular events such as extension of the original thrombus, new emboli in the same territory, 'collateral failure', and blood pressure drops further contributing to hemodynamic compromise [2, 7, 33]. We will now review the available evidence regarding these two main eventualities.

Tissue-based mechanisms

In one large cohort, hyperglycemia was an independent predictor of unexplained END [6], consistent with studies on all-cause post r-tPA END [2, 20]. Several mechanisms might explain this association. First, increased brain lactate production from high circulating glucose could result in severely hypoperfused tissue becoming infarcted [37] and disrupt cell metabolism within mildly hypoperfused tissue, causing it to become symptomatic. Against this scenario, in an RCT insulin therapy did not hamper infarct growth relative to placebo, even though it significantly reduced blood glucose and attenuated brain lactate levels [38]. Second, since stroke patients with high blood glucose receive insulin therapy, occult hypoglycaemic episodes may contribute to unexplained END via neuronal death in the penumbra and oligaemia [39]. However, one recent study failed to document hypoglycaemic episodes in relation to unexplained END [6]. Finally, hyperglycemia has prothrombotic effects [40], which are known to hinder recanalization after r-tPA [41] and might perhaps also facilitate thrombus extension (see in the following).

We are not aware of any study that assessed the relationship between unexplained END and hyperthermia or oxygen saturation, two physiological variables that may increase neuronal death in mildly hypoperfused tissue. Of note, numerous articles report a strong association between admission hyperthermia or proinflammatory markers and all-cause END, but these studies included ENDs beyond 24 h, and unexplained END was not specifically studied [42].

Another potential cause of unexplained END is 'reperfusion injury', defined as "a biochemical cascade causing a deterioration of ischemic brain tissue that parallels and antagonizes the beneficial effect of recanalization" [43]. Although sICH is considered by some as part of reperfusion injury, by definition, it would not rate as unexplained END. Reperfusion injury refers to secondary processes

affecting the neurovascular unit, including poor capillary reperfusion ("no-reflow phenomenon"] and damage to the salvaged penumbra from blood–brain barrier leakage, inflammation, and oxygen radical generation. Although documented in stroke models [43, 44], reperfusion injury has not been linked to secondary neurological deterioration but rather to sub-optimal recovery, or in the case of no-reflow, to lack or poor recovery despite recanalization ('futile recanalization') [45]. Indeed, on a theoretical basis, to cause END, reperfusion injury would need to affect previously 'asymptomatic' tissue—i.e., benign oligemia, whereas it is assumed to affect the 'symptomatic' ischemic penumbra [32]. Furthermore, even if it did affect the oligemia, it would at best account for a small minority of unexplained ENDs as the latter is strongly associated with lack of recanalization [6]. Accordingly, to our knowledge, no published study so far has claimed a link between reperfusion injury and unexplained END.

Vascular events

Three radiological variables have recently emerged as being significantly associated with unexplained END, supporting the pivotal role of cerebral hemodynamic compromise as the main underlying mechanism. The first radiological variable is proximal arterial occlusion on admission workup, which was recently shown to be a strong predictor of unexplained END following r-tPA [6], consistent with studies on all-cause END [2, 46] and on END in non-thrombolyzed mild stroke using slightly wider time frames [17, 18]. The second variable is large admission diffusion/perfusion mismatch (i.e., large penumbra), documented as a predictor of post r-tPA unexplained END in a large study [6]. This observation has subsequently been confirmed in a large study on 464 consecutive r-tPA treated patients, albeit mixing all-case ENDs (note however that ~70% of all ENDs had no clear mechanism in this cohort) [20]. The third radiological variable is no recanalization on follow-up imaging, which was also found strongly associated with unexplained END [6], consistent with data on studies on all-cause ENDs [2]. These associations are of particular interest, since AIS patients with proximal occlusion and perfusion/diffusion mismatch derive the highest benefit from early revascularization therapy [47], further highlighting the ambiguous predictive value of the perfusion/diffusion mismatch [48], which both predicts favorable outcome in the setting of recanalization and unexplained END (and hence poor outcome) in the absence of recanalization.

The above associations support the idea that unexplained END tends to occur in patients with severely affected cerebral perfusion pressure, and may be linked to secondary hemodynamic worsening. This then raises the question as to why should cerebral perfusion pressure worsen? Several possible mechanisms have been proposed.

Collateral failure

Cerebral collateral circulation, which widely differs among individuals, is the alternative vascular network that provides residual blood flow to ischemic areas downstream of an arterial occlusion. The potential role of the collateral circulation to predict unexplained END has never been studied so far, but patients with unexplained END have been found to more likely have a low NIHSS and high perfusion/diffusion mismatch on admission [6, 20], suggesting good initial collateral status. Consequently, 'collateral failure', defined as 'insufficient endurance' of collateral circulation to maintain cerebral perfusion pressure, has been proposed as a potential mechanism of unexplained END [49]. However, collateral failure as a primum movens of cerebral perfusion worsening has not been proven so far, and should be distinguished from secondary collateral failure. For instance, any mechanism that leads to worsening of cerebral perfusion pressure (CPP) could cause secondary 'collateral failure'. Thus, Campbell et al. reported that 'collateral failure', as defined by lower collateral grade on MR-based collateral maps performed 3–5 days post-AIS relative to admission MR, was associated with infarct growth [50]. However, as acknowledged by the authors, the observed association between infarct growth and collateral shifts does not prove causality, i.e., 'collateral failure' could be the consequence—and not the cause—of infarct growth [50].

Additional potential causes for 'collateral failure' include collateral vessel thrombosis (see in the following) and intracranial pressure elevation [51–53], but there is no direct evidence for these mechanisms so far. However, recent animal studies have suggested that intracranial pressure elevations may exist even following minor AIS, reaching a peak ≈24-h post stroke onset [52], which in turn would cause a reduction in collateral flow [51]. However, the mechanism underlying this phenomenon, and whether it exists at all in man, is unknown.

Blood pressure (BP) drops

Systemic BP drops leading to reduction of CPP could also underlie 'unexplained END'. Indeed, CPP represents the difference between systemic BP and cerebral venous pressure, and the role of systemic BP becomes particularly important whenever large volumes of hypoperfused but still viable tissue, vulnerable to minor changes in systemic BP, is present. In this case, any drop in BP would not be compensated by autoregulatory mechanisms, which may in turn lead to oligemic tissue progressing to penumbra and in

turn to infarction. However, BP changes within the first 24 h have not been found to be associated with unexplained END so far [2, 6], although this hypothesis should be prospectively addressed in the future.

Thrombotic factors

In situ extension of the original thrombus or new embolic events in the same territory is attractive hypotheses to explain secondary hemodynamic compromise, via occlusion of previously unaffected perforators, branches, or collaterals. This scenario is illustrated in Fig. 2. To test this hypothesis, we compared the incidence of the susceptibility vessel sign (SVS, a specific marker of thrombus on T2* MR [54]) extension—defined as any new occurrence or extension of SVS from admission to 24-h follow-up MRI—in 22 patients with unexplained END vs. 98 no-END controls, all without 24-h recanalization [8]. In this study, SVS extension was significantly more frequent in the unexplained END than in the no-END group (59 vs. 29%, respectively), suggesting in situ thrombus extension or re-embolization. However, this association does not prove causality, and some unidentified confounding factor might cause both END and thrombus extension. SVS extension in persistent occlusion had been previously reported in two small-scale studies, but neither mentioned whether END occurred in relation to this radiological finding [55, 56].

Our observation is, however, consistent with a pre-thrombolysis era study, where conventional angiography was obtained both before and after neurological deterioration occurring during the first days, and which reported various angiographic changes such as thrombus extension and re-embolization [57]. However, the association between these changes and neurological deterioration could only be inferred from this study as a control group (i.e., nondeteriorating patients) was not included for comparison.

The exact underlying processes that may lead to thrombus extension remain speculative, since no study has examined this specific point so far. We propose that thrombus extension might be due to in situ extension of the original thrombus, caused by abnormal thrombotic pathways, such as increased coagulation activity and resistance to fibrinolysis, or by activation of the physiological coagulation cascade because of blood stasis adjacent to the original thrombus. In support of the latter hypothesis, Qazi and co-investigators recently reported that patients with poor baseline collaterals had longer clots than those with intermediate or good collaterals [58]. Alternatively, proximal thrombus extension could be explained by re-embolization in the same territory. Supporting this mechanism, Vanacker et al. reported END in 2/7 r-tPA treated patients with free-floating thrombus in the cervical carotid artery. Follow-up 24-h imaging showed complete disappearance of the floating thrombus, consistent with re-embolization [59]. Another study found that large-artery atherosclerosis was an independent predictor of unexplained END [5], consistent with two studies on all-cause END [20, 46], again favouring re-embolization from an unstable plaque.

In line with the thrombotic hypothesis, use of aspirin prior to stroke onset was found in one large study to protect against unexplained END [6]. Another study reported a similar association with all-cause ENDs [14]. Thus, antiplatelets may protect against both thrombus extension and same-territory recurrent embolization.

Table 1 summarizes the predictors, associated factors, and putative underlying mechanisms of unexplained END.

Management of unexplained END

Reversal of unexplained END

The acute management of END obviously depends on its underlying cause. Whenever END occurs, immediate review of BP, temperature, glycaemia, and oxygen saturation is mandatory, as well as brain and vascular imaging. Although published guidelines exist for sICH and malignant edema [4], no guidelines or recommendations exist for unexplained END, and hence, no clear action is usually taken to revert the deficit. Medical treatment following unexplained END may involve approaches such as plasma volume expansion, induced hypertension, intensified antiplatelet therapy, and acute anticoagulation, but none has been formally tested so far. Recently, a retrospective study found that urgent rescue endovascular therapy following END in minor AIS was feasible and may provide better outcomes [60]. However, though endovascular therapy led to better outcomes overall, half of the END patients still had poor functional outcome. RCTs would be required to assess this therapeutic option.

Prevention of unexplained END

Preventing unexplained END is probably the best approach. Considering the apparent major role of hemodynamic and thrombotic factors, ensuring early recanalization and/or preventing thrombus extension and re-embolization would be appropriate measures. However, no RCT so far has assessed the effect of revascularization therapy (r-tPA and/or MT) on unexplained END. However, a recent retrospective study on minor AIS with proximal occlusion reported a twofold lower rate of all-cause END and better overall outcomes with revascularization therapy (r-tPA alone or endovascular therapy) as

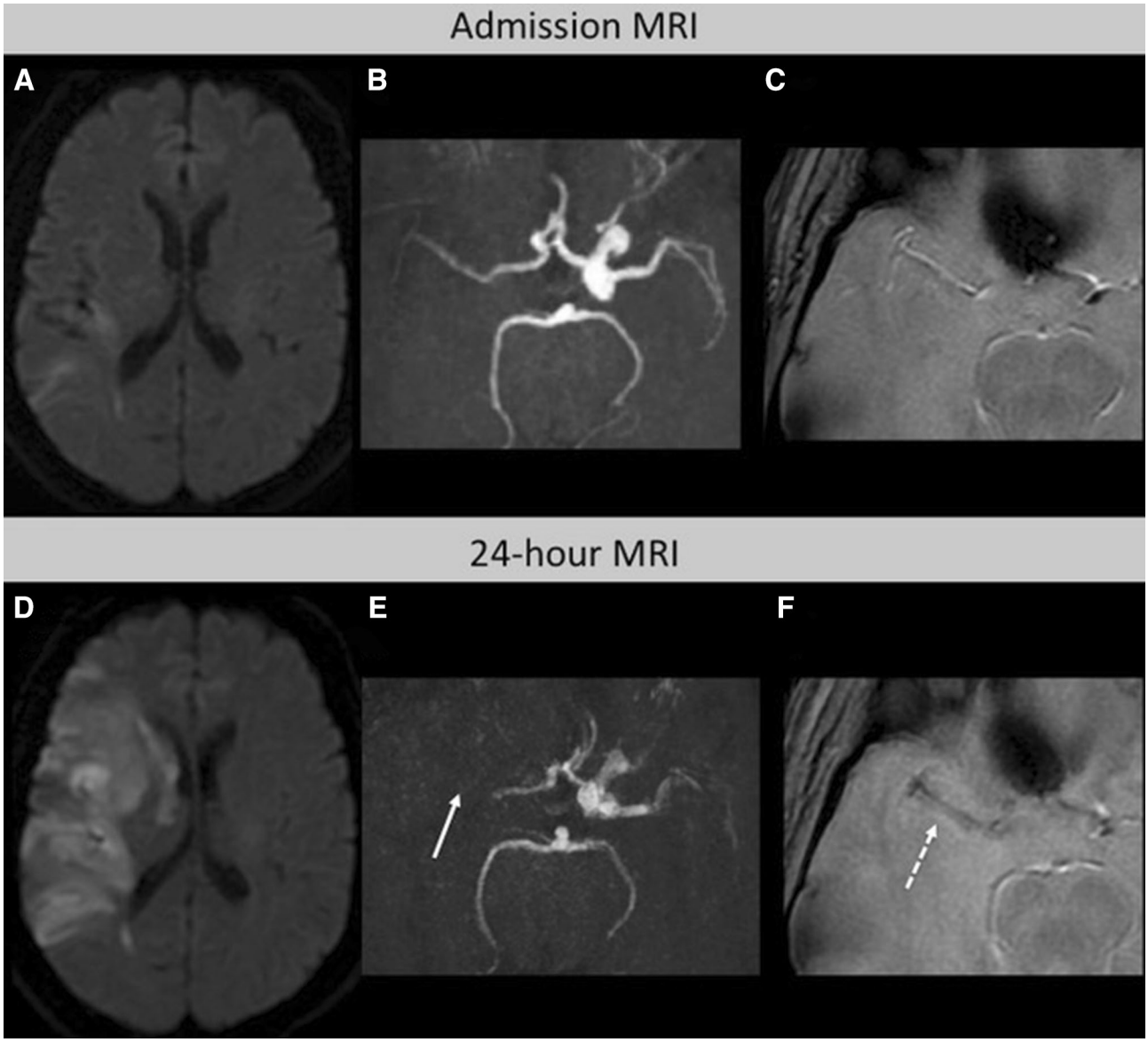

Fig. 2 Illustrative case of thrombus extension in an unexplained END patient. A 68-year-old patient was admitted with left-sided hypoesthesia, hemianopia and neglect; NIHSS was 5. Admission MRI (*upper panel*) showed a small right superficial MCA infarct on DWI (**a**) and tandem intracranial carotid–distal MCA occlusion (**b**), the latter also visible on GRE/T2* (not shown). Note that the proximal MCA was patent (**b**), without any susceptibility vessel sign (SVS) on GRE/T2* (**c**). He experienced a severe END 16 h following r-tPA, with occurrence of left hemiparesis and worse neglect (NIHSS 19). 24-h follow-up MRI showed marked extension of the DWI lesion (**d**) and SVS extension occluding the proximal MCA (**e**, **f**)

compared to no recanalization therapy [15]. In addition, no study so far has assessed the incidence of unexplained END in r-tPA vs. MT-treated samples, although lower rates of unexplained END would be expected with the latter given the much higher rates of early recanalization. Other therapeutic interventions aiming to improve tissue perfusion via collaterals have recently been or are currently being studied, such as induced hypertension, lying with head-up position, volume expansion, external counterpulsation, partial aortic obstruction, and sphenopalatine ganglion stimulation [61].

Regarding prevention of thrombus extension and re-embolization, the findings reported above would speak for administering anti-platelet agents as early as possible after r-tPA. However, a post hoc analysis of the ARTIS trial, an RCT in an unselected AIS population comparing ultra-early (within 90 min of the start of r-tPA) addition of aspirin after r-tPA vs. r-tPA alone recently found that aspirin increased the risk of END due to sICH, and had no effect on incidence of unexplained END [62]. Although this finding calls for caution, the retrospective analysis and the ultra-early timing of aspirin administration need to be

Table 1 Predictors, associated factors, and putative underlying mechanisms of unexplained END

Admission predictors of unexplained END [reference]	OR (95% CI)	Putative underlying mechanism
NIHSS [6]	0.89 (0.82–0.96)[a,b]	N/A
Prior use of antiplatelets [6]	0.22 (0.06–0.85)[a,d]	Prevention of thrombus extension/re-embolization
Glycemia [6]	1.26 (1.06–1.44)[a,e]	Neuronal survival in oligemic areas
Proximal arterial occlusion [6]	6.55 (1.50–28.57)[c]	Hemodynamic compromise
Large perfusion-diffusion mismatch [6]	1.12 (1.01–1.25)[c]	Hemodynamic compromise

Associated factors of unexplained END on follow-up imaging [reference]	OR (95% CI) or *P*	Putative underlying mechanism
Extra-penumbral extension of DWI lesion [7]	$P = 0.047$[c]	Final common pathway
No-recanalization [6]	4.18 (1.28–13.69)[a]	Hemodynamic compromise
Susceptibility vessel sign extension [8]	3.96 (1.25–12.53)[a]	Thrombus extension/re-embolization
Large-artery atherosclerosis [5]	3.8 (1.6–9.3)[a]	Re-embolization

[a] Multivariate analysis

[b] Per 1 point increase

[c] Univariate analysis

[d] Per 10 ml increase

[e] Per 1 mmol/l increase

considered. Thus, this approach remains of interest and should be tested using an appropriate trial design, selecting populations at high risk of unexplained END based on the above-described predictors. As a downside, the number of patients needed to be assessed in such a study would likely need to be very large to expect a clear answer. Finally, the option of early anticoagulation to prevent unexplained END has not been tested so far, but the high risk of sICH should be considered.

Conclusion

END occurring within 24 h of AIS is not an uncommon event, is predictive of a poor 3-month outcome, and has no clear cause in the majority of cases. Although based on a limited number of small-scale studies, extension of symptomatic tissue appears to subtend most instances of unexplained END, with vascular events such as thrombus extension and re-embolization likely the main underlying mechanisms. Further work using rigorous operational and clinically relevant definitions is required to establish the mechanisms underlying unexplained END, both in thrombolyzed and non-thrombolyzed populations, as well as after MT. To enhance the chance of success, comprehensive serial vascular, thrombus, collateral and perfusion imaging, as well as intensive/continuous physiological monitoring, should be implemented. In line with the putative underlying mechanisms, curative interventions such as rescue MT would be important to test. Prevention of unexplained END, particularly in the minor stroke setting, is a priority research area, and apart from more widely implementing MT, one might consider earlier introduction of anti-platelet agents following r-tPA than currently recommended (i.e., 24–48 h after stroke onset), which should be prospectively tested in populations at high risk of unexplained END.

Compliance with ethical standards

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Conflict of interest The authors have no conflict of interest to declare.

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