Emerging evidence in the diagnosis and management of carotid near-occlusion

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Abstract:

Carotid near-occlusion (CNO) is a form of carotid disease with severe internal carotid artery (ICA) stenosis and a significantly reduced lumen diameter distal to the stenosis. CNO is characterised as either having distal complete, thread-like, lumen collapse or not and is referred to as CNO with or without full collapse, respectively. Diagnosis has been traditionally performed with Digital Subtraction Angiography (DSA) using four angiographic criteria. However, the delayed phase of multiphase Computed Tomography Angiography (CTA) has largely replaced DSA and it is currently the CNO imaging of choice. Ultrasonography may also help in detecting low flow velocity. CNO has been under-reported in clinical practice and its optimal treatment is still debated, while contradicting evidence has been reported concerning the association between CNO and significant risk of stroke. The most recent 2023 ESVS guidelines suggested that intervention is not recommended for symptomatic CNO patients, unless as part of a randomised controlled trial, while for recurrent symptoms, intervention may be considered only after multidisciplinary team review. However, this recommendation was mainly based on a post-hoc analysis of pooled data from NASCET and ECST trials, performed in the 1990s. Recent studies have also provided various results, which are partly attributed to the lack of clear CNO definition, heterogeneous cohorts and inadequate discrimination between CNO with and without full collapse. Our review presents an overview of the current evidence for the diagnosis and treatment of patients with CNO.

Keywords: carotid, near-occlusion, diagnosis, management

INTRODUCTION

Carotid near-occlusion (CNO) is part of the spectrum of severe carotid stenosis, where the internal carotid artery (ICA) distal to the stenosis appears diminutive, in contrast to more common ICA stenosis, which does not result in diameter decrease of the distal ICA[1]. CNO is characterized as either having complete distal, thread-like, lumen collapse or not and is referred as CNO with or without full collapse, respectively[2]. CNO was initially reported by Lippman et al. in 1970[3] and has since been reported using a variety of nomenclature.

Despite being recognized as rare, CNO is more prevalent among symptomatic patients with ≥50% ICA stenosis[1]. The European Carotid Surgery Trial (ECST) and the North American Symptomatic Endarterectomy Trial (NASCET) post-hoc analyses demonstrated that individuals with symptomatic CNO would not benefit from surgery and that their risk of recurrent stroke might be lower than that of patients with severe ICA without near-occlusion. However, these trials were conducted in the 1990s and it is debatable whether their results are still valid today. Although recent evidence has linked symptomatic CNO to an elevated risk of ipsilateral hemisphere stroke, large prospective studies to ascertain the exact risk of recurrent stroke among these patients are currently lacking[2]. Even the most recent prospective Randomised Clinical Trials (RCTs), such as the International Carotid Stenting Study (ICSS) and the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) did not recruit patients with symptomatic CNO[4]. As a result, there is lack of evidence to support or reject revascularization in patients with CNO, and the optimal management is still debatable. Our study aimed to perform an overview of the current evidence for the diagnosis and treatment of patients with CNO.

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OTHER TERMS FOR CNO

Various terms have been used to describe CNO, such as near total occlusion, pseudo-occlusion, string sign, slim sign, critical stenosis, small or narrow distal ICA, pre-occlusive stenosis, subtotal stenosis, subtotal occlusion, functional occlusion, sub-occlusion, 99% stenosis, hairline residual lumen and incomplete occlusion[5]. Due to similarities with other ICA pathologies causing distal lumen collapse, some authors proposed the term “atheromatous pseudo-occlusion” to separate CNO

from other non- atherosclerotic entities, such as dissection, hypoplasia or post-radiation lesions[6]. In line with this, the use of "string sign" should be also discouraged, as it was originally defined for describing dissection[7].

EPIDEMIOLOGY AND NATURAL HISTORY

CNO has been reported with a prevalence of less than 10% among patients with significant ICA stenosis[8] and approximately 3% among symptomatic patients[2]. A total of 40% of these patients will present with ICA occlusion within 12 months. More specifically, progression from discovery to total occlusion with best medical therapy (BMT) has been estimated at 16 per 100 person-years[9]. However, our knowledge of exact CNO's natural history is limited. Previous studies described rates of progression to occlusion between 26-37% per year[10]. In a recent study, almost a third of patients with CNO progressed to complete occlusion at 24 months follow- up. The proportion of symptomatic progression to complete occlusion was 17.5% of the patients who presented with ipsilateral symptoms[10]. This can be attributed to collateral brain network and effective autoregulation of the cerebral circulation that adapts for the chronically diminished blood flow[10].

PATHOPHYSIOLOGY OF STROKE IN CNO PATIENTS

Although not clearly investigated, the pathophysiological mechanism of stroke among CNO patients could be attributed to ICA progression to occlusion. However, a recent study failed to identify fully collapsed symptomatic near-occlusions which progressed to occlusion[7]. Hemodynamic and embolic mechanisms have also been investigated. Progression of ICA near occlusion to complete occlusion may lead to decreased perfusion of the ipsilateral hemisphere blood supply from the ICA, depending its perfusion from collaterals, which in turn may stimulate blood stagnation, increased risk of thrombus formation and eventually to embolization to intracranial collaterals[11]. Interestingly, some near-occlusions can represent recanalized thrombotic occlusions with risk for embolic events.

THE CORRELATION OF HIGH RISK OF ISCHEMIC STROKE AMONG CNO PATIENTS IS STILL UNDER INVESTIGATION

Contradicting evidence has been reported concerning the association between CNO and significant risk of stroke. Since there was a comparatively low long-term risk of stroke in the medical arm, carotid endarterectomy (CEA) did not significantly improve outcomes among patients with CNO without full collapse in the NASCET and ECST trials. While these trials reported a relatively low risk of recurrent stroke in the medical arm, a recent study indicated a significant risk of recurrence across patients with CNO[12]. A possible explanation is the disparity in timing of intervention. These trials frequently included near-occlusion patients with a significant delay (> 4 weeks) after the last incident. Another explanation is that the higher risk in recent studies may be due to risk difference between CNOs with and without full collapse. The authors noted that a large number of high-risk CNO patients with full collapse were initially misdiagnosed as occlusions in routine practice imaging, but were correctly identified by the experts. In addition, a large number of the high-risk near-occlusions, which were later deemed technically untreatable, had a significant risk of stroke when intervention was attempted[12].

In line with the above, another recent study found increased risk of recurrent ipsilateral ischemic stroke in the early days following the presenting episode in CNO patients. The stroke rate among patients with CNO with full collapse was 18%, whereas the respective risk in patients without full collapse was low[1]. We believe that the reason of the difference in the rate of stroke recurrence among the various studies, is the unclear distinction between outcomes of CNO patients with and without full collapse. This is independent of the progression to complete occlusion, as also pointed by a recent study[7].

Similarly, other studies showed increased risk of recurrent stroke with a cumulative annual incidence of ipsilateral ischemic stroke of 14% and ipsilateral transient ischemic attack (TIA) of 24% in the group of patients who received medical treatment[4]. This was also confirmed by our previous systematic review on the topic. We found that BMT was presented with almost three-fold higher stroke IR per 100 person-years compared to carotid endarterectomy or stenting[13]. However, it should be highlighted that the suggested BMT is improved significantly over the past 20 years, thus we cannot exclude lower stroke risk in the future studies' medical treatment arms.

DIAGNOSIS

CNO with full collapse can be recognised as a thread-like appearance of distal ICA, which responds to reduction in flow[5], whereas less severe flow reduction leads to a "normal-appearing" but small distal artery (near-occlusion without full collapse) (1). Although seems clear, CNO can be misdiagnosed to conventional stenosis with suboptimal imaging and interpretation[5].

Digital Subtraction Angiography (DSA) is the gold standard

DSA has been the gold standard for the diagnosis of CNO. Four angiographic criteria were suggested by Fox et al.[14]: (I) reduction in ICA diameter compared with the ipsilateral external carotid artery (ECA), (II) obviously reduced diameter of the ICA compared with the opposite ICA, (III) intracranial collaterals seen as a cross-filling of contralateral vessels or ipsilateral contrast dilution and (IV) delayed cranial arrival of ICA contrast compared with that of the ECA. Two of the 4 criteria are required for diagnosis. However, the clinician should not overestimate CNO without full collapse, because the relatively small size of a distal ICA with a larger contralateral ICA can be an anatomic variation. Other variations that should be noted is diversity in ICA size depending on circle of Willis variations, or a single ICA supplying both anterior cerebral arteries[5,11]. It is also important to differentiate CNO from long distal ICA tapering of dissection, as the later do not show a prominent ICA bulb stenosis or true ICA hypoplasia which shows a tiny bony carotid canal[5,11]. Differentiating CNO from occlusion is also very important. Delayed angiography may be useful to detect delayed contrast through a severely collapsed artery.

Differentiating CNO with and without full collapse is also of paramount importance and it is based mainly on the "thread-like" distal ICA lumen[5,11].

Diagnosis with ultrasonography

Ultrasound can be also important for the diagnosis of CNO. The main characteristic is the presence or absence of blood flow. CNO with full collapse can be seen as **a** very tight stenosis with a minimal flow channel, slow flow velocities and a grossly pathologic flow profile or dampened, pseudo-venous flow with low pulsatility. The best stenosis PSV threshold for "low velocity" is likely slightly above 125 cm/s. However, when it comes to CNO without full collapse, differential diagnosis from conventional high grade ICA stenosis is difficult, as both have high flow velocities. In that case, Power Doppler, contrast-enhanced sonography and/or transoral sonography to also assess distal artery patency at the level of the pharynx may be useful adjuncts [5,11,15]. However, given the difficulty in diagnosis CNO with ultrasound in the every-day practice, its diagnostic accuracy is still limited.

Diagnosis with Computed Tomography Angiography (CTA)

CTA is probably the most important and useful tool for the diagnosis of CNO. Bartlett et. al.[16] proposed CTA-specific diameter-measurement criteria for the diagnosis of CNO: 1) stenosis diameter of ≤1.3 mm, 2) ipsilateral distal ICA diameter of ≤3.5 mm, 3) ipsilateral distal ICA/contralateral distal ICA ratio of ≤0.87 and 4) ipsilateral distal ICA/ipsilateral ECA of ≤1.27. Interestingly, a recent validation study included patients with CNO, severe ICA stenosis and ICA occlusion and compared the diagnostic accuracy of CTA with DSA among many studies[17]. The most accurate criteria were i) distal ICA diameter less than or equal to the ipsilateral ECA, ii) ICA to ECA comparison of diameter reduction and iii) the ratio of the distal internal carotid artery (ICA) diameter to that of the contralateral distal ICA ≤ 0.87[17].

Magnetic Resonance Angiography (MRA) for the diagnosis of CNO

MRA is not very popular for the diagnosis of CNO. Slow-flow signal is below the visibility threshold in TOF MRA, while the flow gap is almost identical in CNO with and without full collapse. However, when found, segmental flow gaps may suggest vessel patency, because occlusions are more likely to show full length signal absence[5,11].

Recommendation for diagnosis of CNO

CTA is suggested for current CNO diagnosis. Delayed phase of multiphase CTA imaging is mandatory, mainly as a routine postcontrast head CTA looking for a late, slow-flowing collapsed ICA lumen at the skull base or carotid canal. Other relative measurements necessitate a comparison, but this comparison may occasionally be deceptive since, for example, bilateral CNO affects ICA ratio and ECA sizes. Ultrasonography, although not definite, may also help in detecting low flow velocity.

PRACTICE GUIDELINES FOR THE MANAGEMENT OF CNO

Recent guidelines have commented for the management of patients with CNO. Among them, the 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)[18], suggested that *"carotid endarterectomy or carotid stenting are not recommended in symptomatic patients with a chronic internal carotid near-occlusion, unless associated with recurrent ipsilateral symptoms (despite optimal medical therapy) and following multidisciplinary team review"*. Moreover, the 2021 Society for Vascular Surgery (SVS) Guidelines did not discriminate treatment between high grade and CNO patients[19]. Even recently, the 2023 ESVS guidelines stated that *"for symptomatic patients with carotid near occlusion and distal vessel collapse, carotid endarterectomy and carotid stenting are not recommended, unless as part of a randomised controlled trial"* and that "*for patients with carotid near occlusion and distal vessel collapse with recurrent carotid territory symptoms (despite best medical therapy), carotid endarterectomy or carotid artery stenting may be considered only after multidisciplinary team review*"[20].

CRITIQUE ON THE RECENT PRACTICE GUIDELINES FOR THE MANAGEMENT OF CNO

It is evident that recent guidelines suggested a rather conservative treatment of patients with CNO. However, this recommendation is mainly based on a post hoc reanalysis of pooled data from NASCET and ECST. This data, although coming from RCTs, are probably outdated for the following reasons. BMT included only aspirin therapy in varying doses and antihypertensive treatment, whereas now medical therapy has improved significantly. An intention-to-treat analysis was used in NASCET, which might have underestimated the benefit of CEA in CNO patients, due to the high crossover rate during follow-up in the BMT group. The lower stroke risk in the BMT group may have been attributed to the lower prevalence of some risk factors, such as older age, diabetes, ischaemic heart disease and hyperlipidaemia in ECST. Timing is also very important. Only 35-45% of the patients were randomized within the first month, in which the benefit of intervention is the largest. Moreover, it is likely that large number of patients with chronic CNO were also included in these trials, and such patients may benefit more from BMT, compared to the patients with an acute CNO[8]. What is more, 94% of CNO patients included in these trial did not have full collapse[21]. Far less, patients with CNO were excluded from recent RCTs such as the CREST and the ICSS. It is therefore important to update our current knowledge with new prospective RCTs, incorporating patients with CNO with and without full collapse.

RECENT EVIDENCE AND CONTROVERSIES

Despite the fact that recent guidelines pointed to BMT for patients with CNO, current non-randomized studies are presenting with various results. A recent meta-analysis showed that BMT was not superior to CEA or CAS with respect to 30-day or 1-year stroke or death prevention[8]. The authors found that the risk of stroke or death within 30 days after intervention was very low (1.8% after CEA and 2.2% after CAS), that the

BMT group was not optimized in terms of antiplatelet, statin and antihypertensive treatment and that it is still room for improvement of BMT in future studies.

A recent multicentre registry study showed that the risk of early recurrent stroke may be higher in BMT with symptomatic CNO[4]. This, along with the good results with CAS or CEA in CNO patients[22,23] might indicate that BMT is not a better choice, compared to intervention. A study by Antonopoulos et al.[9] also found low stroke rates after intervention, at 1.52% after CEA and 1.80% after CAS, compared to 8.39% after BMT. Terada et.al.[24] also found good results after CAS, indicating that it may be a good alternative to CEA, given its low risk, high success rate and feasibility. However, it should be highlighted that CAS is best to be performed by an experienced team and with minimum wire manipulations[9].

POINTS OF INTEREST WHEN ASSESSING CNO

Although it seems paradoxical, there is still discrepancy between guidelines and many recent studies concerning the optimal management of patients with CNO. A key point when assessing CNO is the lumen full collapse. A study has found that the 90-day recurrent stroke risk could reach up to 43% in patients with symptomatic CNO with full collapse and 0% for patients without full collapse[7]. Unfortunately, many studies have not separated these two entities (with or without full collapse) as it seems that the possibility of near occlusion without full collapse has not been fully acknowledged[9].

Another interesting point relies on the technique itself. The use of shunt during CEA for CNO is an important factor. The distal ICA may be too thin for proper shunt insertion and it should be probably avoided. In that case, systolic blood pressure should be maintained at increased levels to provide better collateral perfusion. In some other cases, severe concentric or eccentric calcification might hamper stent implantation during CAS and this should be included in the preoperative planning to avoid unnecessary embolic risk[2].

An important issue is also the post-operative management of CNO patients. As pre-operative intracranial perfusion is especially poor among those patients, reperfusion injury is more likely after a successful blood flow restoration to the brain, compared to conventional high grade ICA stenosis. Monitoring with strict blood pressure control is mandatory post-operatively in order to prevent brain oedema and possible intracerebral hemorrhage[2].

CONCLUSIONS

CNO is a frequently overlooked and easily misdiagnosed condition and its treatment strategy still remains debatable. This is partly attributed to the lack of a clear CNO definition, which may have led to heterogeneous cohorts and results among the various reports. Another relevant unsolved issue is the proper identification of CNO, as there is no easily applicable diagnostic modality with high diagnostic accuracy. Moreover, the exact mechanism, hemodynamic, embolic, by which the presence of full collapse may lead to an increased risk for ipsilateral stoke is still not well understood. The potential benefit of intervention in CNO patients is also not clearly depicted from the literature. As a result, identification of high-risk CNO patients that may require intervention is of paramount importance. Future RCTs should be designed to proper addressed these issues[25].

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