Lysophosphatidylcholine to stratify risk of ischemic stroke in TIA

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Neurology® 2015;84:17–18

TIA portends an increased risk for ischemic stroke. This risk can be reduced by >50% with early implementation of stroke prevention therapy.[1] Stroke risk in TIA can be estimated using the ABCD2 score, diffusion-weighted imaging (DWI), and presence of large arterial atherosclerosis (LAA).[2] However, not infrequently TIAs deemed to be low risk precede stroke and TIAs deemed to be high risk do not. Thus additional methods to stratify stroke risk in TIA are needed.

In this issue of *Neurology*®, Jové et al.[3] evaluated plasma metabolites to predict stroke risk in TIA. Plasma was obtained within 24 hours of TIA and molecules soluble in methanol were analyzed by high performance liquid chromatography–mass spectrometry (HPLC-MS). A total of 293 TIAs were studied and divided into 2 cohorts (first cohort n = 131, second cohort n = 162). The median ABCD2 score was 5.1 (4.0–6.0), 40.9% had positive DWI, and 22.3% had LAA. Follow-up occurred at 7 days, 90 days, 6 months, and >1 year. Over this time period, 35 patients (11.9%) had ischemic stroke, 15 (5.1%) of which occurred within 90 days. Recurrent stroke was associated with higher ABCD2 and LAA.

TIAs with recurrent stroke had differences in several metabolites including increased myristoylethanolamine and decreased levels of 1-monopalmitin, dodecanoic acid, meso-erythritol, threonate, and lysophosphatidylcholine LysoPC(16:0) (16 denoting the number of carbons in the fatty acid chain and 0 the number of double bonds) ($p < 0.05$). Of these metabolites, LysoPC(16:0) was confirmed in the second TIA cohort. However, on prediction analysis, LysoPC(16:0) did not add to the predictive ability of the ABCD2 or ABCD2–LAA scores. When all TIAs were analyzed, LysoPC (20:4) was decreased in those with recurrent stroke ($p < 0.05$) and found to increase the predictive ability of the ABCD2 and ABCD2–LAA scores from 64% to 71%, and improve the net reclassification of stroke risk (net reclassification improvement 0.48, $p = 0.0004$).

This study raises the question as to why LysoPCs might be associated with stroke risk in TIA. They act on G-protein–coupled receptors to initiate downstream signaling. Increased levels of LysoPCs are associated with carotid atherosclerosis, oxidized low-density lipoprotein, cerebral ischemia, and activation of inflammatory cells.[4–7] LysoPCs are formed via the enzymatic activity of phospholipases including lipoprotein-associated phospholipase A2 (Lp-PLA2). Of interest, Lp-PLA2 has been associated with stroke risk in TIA as well as stroke, supporting the role of LysoPCs in stroke risk.[8,9]

The study also found 14 metabolites to be different between those with early stroke (0–90 days, n = 15) and those with late stroke (>90 days, n = 20), including decreased arachidonic acid and increased DL-ornitine, epinephrine, glutamine, and vitamin E ($p < 0.05$).[3] LAA is an important cause of early stroke recurrence in TIA. In the current study, LAA accounted for 72% of strokes at day 7, 56% at day 90, and 52% at 1 year.[3] In contrast, cardioembolism was the cause of stroke in 9% of strokes at day 7, 21% at day 90, and 26% at 1 year. Thus, metabolites that differ by time of recurrent stroke may reflect differences in stroke etiology and highlight aspects of arterial disease important to early stroke risk. Several metabolites were specifically increased in TIAs with LAA including androsterone, stearic acid, ascorbic acid, and LysoPC(22:6) ($p < 0.05$). How these metabolites relate to early risk of stroke and atherosclerotic plaque rupture warrants further investigation.

Ideally, a tool to stratify stroke risk in TIA will be rapid and easy to perform as strokes often occur within the first 48 hours of TIA and there is a need to make urgent treatment decisions to prevent stroke. For plasma metabolites to be useful in TIA stroke risk stratification, additional studies will be required to determine how metabolites measured by HPLC-MS can translate into real-time assays for TIA.

This study focused on high-risk TIAs with a median ABCD2 score of 5.1.[3] TIAs with ABCD2 <4 are also

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important to risk stratify, and further evaluation of metabolites in this group is required. In the current study, DWI lesions were present in over 40% of TIAs. In contrast to prior studies,[2] DWI was not associated with increased risk of future stroke. The reasons for this finding are unclear but may relate in part to a mean time to MRI of 3.7 days. Given that many recurrent strokes occur within the first 48 hours, some early strokes may have been missed or inadvertently classified as DWI-positive TIA.

The evaluation of metabolites in TIA is novel and holds promise to identify markers to stratify stroke risk. The many strengths of the study include use of authentic standards to confirm metabolite identity, in-person follow-up with imaging confirmation of stroke, and comparison of metabolites to the ABCD2 score and LAA. There are limitations that compel consideration. The number of TIAs with recurrent stroke was small. Thus, evaluation in larger cohorts is required to confirm findings. The relationship of plasma metabolites in TIA to other factors that might influence their levels such as diet, medications, and plasma protein levels also warrants study. Finally, some metabolites that may be important to stroke risk in TIA may not have been identified because current mass spectrometry databases remain incomplete.

Stroke risk following TIA is commonly estimated using the ABCD2 score in combination with DWI and LAA. Improved understanding of this risk will help to gain insight into the mechanisms behind this risk and allow better clinical risk stratification in TIA. The current study suggests that several plasma metabolites including LysoPC are associated with increased stroke risk in TIA. With further evaluation, metabolomics and other -omic[10]–derived biomarkers are likely to improve stroke risk stratification in TIA. Such markers may also provide insight into the molecular factors important to stroke risk that may serve as targets to better prevent stroke.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet 2007;370:1432–1442.
2. Merwick A, Albers GW, Amarenco P, et al. Addition of brain and carotid imaging to the ABCD(2) score to identify patients at early risk of stroke after transient ischaemic attack: a multicentre observational study. Lancet Neurol 2010;9:1060–1069.
3. Jové M, Mauri-Capdevila G, Suárez I, et al. Metabolomics predicts stroke recurrence after transient ischemic attack. Neurology 2015;84:36–45.
4. Koizumi S, Yamamoto S, Hayasaka T, et al. Imaging mass spectrometry revealed the production of lysophosphatidylcholine in the injured ischemic rat brain. Neuroscience 2010;168:219–225.
5. Mannheim D, Herrmann J, Versari D, et al. Enhanced expression of Lp-PLA2 and lysophosphatidylcholine in symptomatic carotid atherosclerotic plaques. Stroke 2008;39:1448–1455.
6. Schmitz G, Ruebsaamen K. Metabolism and atherogenic disease association of lysophosphatidylcholine. Atherosclerosis 2010;208:10–18.
7. Zhang Z, Lee YC, Kim SJ, et al. Production of lysophosphatidylcholine by cPLA2 in the brain of mice lacking PPT1 is a signal for phagocyte infiltration. Hum Mol Genet 2007;16:837–847.
8. Cucchiara BL, Messe SR, Sansing L, et al. Lipoprotein-associated phospholipase A2 and C-reactive protein for risk-stratification of patients with TIA. Stroke 2009;40:2332–2336.
9. Delgado P, Chacon P, Penalba A, et al. Lipoprotein-associated phospholipase A(2) activity is associated with large-artery atherosclerotic etiology and recurrent stroke in TIA patients. Cerebrovasc Dis 2012;33:150–158.
10. Jickling GC, Zhan X, Stamova B, et al. Ischemic transient neurological events identified by immune response to cerebral ischemia. Stroke 2012;43:1006–1012.