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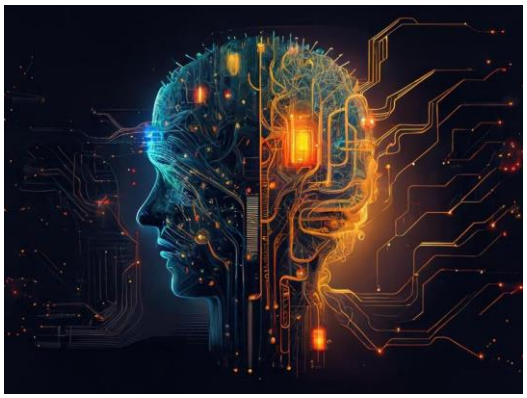
English translation

Clogged ‘drains’ in the brain a likely early-warning sign of Alzheimer’s disease, find NTU Singapore scientists



A research team from the Lee Kong Chian School of Medicine at Nanyang Technological University in Singapore has discovered that the "drainage system" responsible for clearing toxic waste from the brain (i.e., enlarged perivascular spaces) is frequently blocked in patients with pre-Alzheimer's disease. This finding, confirmed through analysis of brain MRI and blood biochemical indicators from nearly 1,000 participants from various ethnic backgrounds in Singapore, shows that the degree of blockage is significantly correlated with core pathological markers of Alzheimer's disease, such as β-amyloid deposition and tau tangles. Furthermore, it is more effective than traditional white matter damage indicators in predicting disease progression earlier, providing new evidence for early screening without additional testing. This is particularly important for Asian populations due to significant differences in the genetic risk characteristics of the disease compared to Western populations.

The research team from Nanyang Technological University in Singapore found that this condition, known as "enlarged perivascular spaces," is likely an early warning sign of Alzheimer's disease, a common type of dementia.

The 'drainage system' responsible for clearing toxic waste from the brain is frequently blocked in patients with pre-Alzheimer's disease. The study, led by Associate Professor Nagaendran Kandiah of the Lee Kong Chian School of Medicine at Nanyang Technological University, states, "Since these brain anomalies can be visually identified

on routine magnetic resonance imaging (MRI) scans performed to evaluate cognitive decline, identifying them could complement existing methods to detect Alzheimer's earlier, without having to do and pay for additional tests."

Justin Ong, a fifth-year student at the medical school and the study's first author, added that early detection of Alzheimer's disease is crucial, enabling clinicians to intervene promptly and slow the progression of cognitive problems such as memory loss, slowed thinking, and mood changes. The study was conducted as part of the Scholarly Project module in the Bachelor of Medicine and Bachelor of Surgery programme at the Lee Kong Chian School of Medicine.

This study is significant because it is one of the few studies globally focusing on Asian populations—most similar studies concentrate on participants of Caucasian ethnicities. The team analyzed nearly 1,000 participants representing Singapore's multi-ethnic population, comparing those without cognitive impairment with those with mild cognitive impairment. Asian studies are particularly crucial because previous research has shown differences in dementia-related symptoms across different ethnic groups.

"For example, among Caucasians with dementia, past studies show that the prevalence of a major risk gene, apolipoprotein E4, linked to Alzheimer's is around 50 to 60 per cent. But among Singapore dementia patients, it is less than 20 per cent, " noted Associate Professor Kandiah, who also serves as the Director of the Dementia Research Centre at the Lee Kong Chian School of Medicine. Therefore, conclusions drawn from studies in Caucasian patients may not be applicable to Asian populations, and vice versa.

Predicting Lesions Before the Onset of Alzheimer's Disease

A space called the "perivascular space" exists around the blood vessels in the brain. Toxic waste products, such as β-amyloid and tau proteins, which are abundant in Alzheimer's patients, are eliminated through this space. If these "drainage channels" become blocked due to a decline in the efficiency of the brain's clearance system, enlarged perivascular spaces, visible on MRI scans, will form. However, it was previously unclear whether this condition was associated with dementia, especially Alzheimer's disease.

A research team at Nanyang Technological University overcame the limitations of earlier studies by comparing more Alzheimer's disease indicators. They compared the blocked brain "drainage channels" with hallmark indicators of the disease—β-amyloid protein and white matter damage (the neural fiber network connecting different areas of the brain).

The study included nearly 1,000 participants in Singapore, including nearly 350 without cognitive problems (whose cognitive abilities such as thinking, memory, reasoning, decision-making, and concentration were normal). The remaining participants exhibited early signs of cognitive disease, including mild cognitive impairment—a stage before the overt onset of dementia. Previous research has shown that individuals with mild cognitive impairment have a higher risk of developing Alzheimer's disease or vascular dementia (dementia caused by reduced blood flow to the brain).

In the latest study, researchers analyzed the participants' MRI scans and found that those with mild cognitive impairment were more likely to have blocked brain "drainage channels"—enlarged perivascular spaces—than other participants. Scientists also tested the participants' blood for seven specific biochemical substances (including β-amyloid protein and tau protein), the presence of which is a warning sign of Alzheimer's disease.

Brain "drainage channel" blockage was significantly correlated with four of the seven measured indicators. This means that individuals with enlarged perivascular spaces are more likely to have abnormally increased amyloid plaques, tau tangles, and brain cell damage in the brain, thus having a higher risk of developing Alzheimer's disease.

Researchers also investigated whether white matter damage (a recognized indicator of Alzheimer's disease) was associated with disease-related biochemicals. They found correlations in six of the seven indicators, but with key differences. When further comparing white matter damage with enlarged perivascular spaces, they found that in participants with mild cognitive impairment, the association between Alzheimer's disease-related biochemicals and enlarged perivascular spaces was stronger than that with white matter damage. This suggests that blocked brain "drainage channels" are an early indicator of Alzheimer's disease.

These findings allow clinicians to more accurately determine the appropriate treatment, delaying and preventing Alzheimer's disease before permanent brain damage occurs. “The findings carry substantial clinical implications,” said Associate Professor Kandiah. “Although white matter damage is more widely used in clinical practice to evaluate for dementia, as it is easily recognised on MRI scans, our results suggest that enlarged perivascular spaces may hold unique value in detecting early signs of Alzheimer’s disease.”

Dr. Rachel Cheong Chin Yee, a Senior Consultant and Deputy Head at Khoo Teck Puat Hospital’s Department of Geriatric Medicine in Singapore, commented that this study reveals changes in small blood vessels in the brain—in this case, enlarged perivascular

spaces surrounding the vessels and helping to clear brain waste—that may contribute to Alzheimer's disease. Dr. Cheong, who was not involved in the study, noted: "These findings are significant because they suggest that brain scans showing enlarged perivascular spaces could potentially help identify people at higher risk of Alzheimer's disease, even before symptoms appear."

Dr. Chong Yao Feng, a Consultant at the National University Hospital's Division of Neurology in Singapore (also a Clinical Assistant Professor at the National University of Singapore's Yong Loo Lin School of Medicine, and not involved in the study), stated that cerebrovascular diseases (conditions that cause problems with blood vessels in the brain) and Alzheimer's disease have traditionally been thought to be caused by different mechanisms. "The study's findings are intriguing as they demonstrate that both diseases do interact in a synergistic manner," Dr. Chong explained. If a doctor orders a brain MRI scan to assess a patient's cognitive symptoms and finds cerebrovascular disease markers such as the enlarged perivascular spaces involved in the NTU study, it shouldn't be attributed solely to vascular problems—because the presence of these markers may increase the patient's risk of also having Alzheimer's disease. "Doctors will then have to use their clinical judgement of the patient's scan and symptoms, as well as discuss with the patient, to determine if more checks are needed to confirm whether a patient has Alzheimer's disease or not," he added.

The Nanyang Technological University research team plans to follow up on study participants and count the number who eventually develop Alzheimer's dementia to verify whether enlarged perivascular spaces can predict that those with blocked "drainage channels" are more likely to progress to dementia. As more studies establish the link between blocked "drainage channels" and Alzheimer's disease in other populations, the detection of enlarged perivascular spaces in future brain MRI scans may be added to the existing clinical toolkit, allowing for earlier determination of whether a patient will develop Alzheimer's disease.

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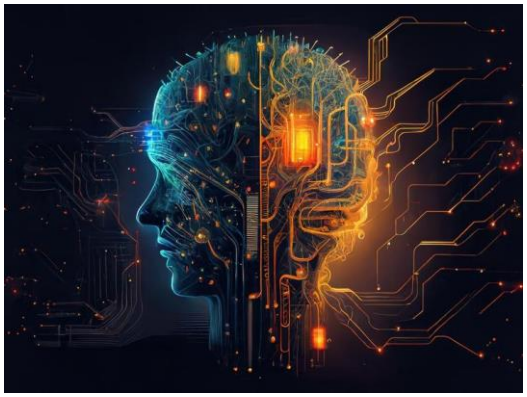
Original text

脑部"排水系统"堵塞或是阿尔茨海默病早期预警信号，新加坡南洋理工大学科学家发现



新加坡南洋理工大学李光前医学院研究团队发现，负责清除大脑有毒废物的"排水系统"（即扩大的血管周围间隙）在阿尔茨海默病前期患者中常出现堵塞现象，该发现通过分析近 1000 名新加坡多族裔参与者的脑部磁共振成像及血液生化指标证实，堵塞程度与 β-淀粉样蛋白沉积、tau 蛋白缠结等阿尔茨海默病核心病理标志物显著相关，且较传统白质损伤指标更能早期预测疾病发展，为临床提供无需额外检测的早期筛查新依据，对亚洲人群尤其重要因该病遗传风险特征与西方存在显著差异。

“负责清除大脑有毒废物的‘排水系统’在阿尔茨海默病前期患者中常出现堵塞现象。”新加坡南洋理工大学研究团队发现，这种被称为“扩大的血管周围间隙”的状况，很可能是阿尔茨海默病的早期预警信号。阿尔茨海默病是痴呆症的常见类型。

南洋理工大学李光前医学院（LKCMedicine）副教授纳根德兰·坎迪亚（Nagaendran Kandiah）领导的该研究指出：“由于这些脑部异常可通过常规磁共振成像（MRI）扫描在评估认知能力下降时直观识别，发现它们能补充现有检测方法，无需额外检测即可更早发现阿尔茨海默病。”

该医学院五年级学生、研究第一作者贾斯汀·翁（Justin Ong）补充道，早期发现阿尔茨海默病至关重要，这能让临床医生及时干预，延缓患者记忆力减退、思维迟缓和情绪变化等认知问题的恶化。该研究作为李光前医学院医学学士和外科学士课程中学术研究模块的一部分开展。

该研究意义重大，因其是全球少数聚焦亚洲人群的研究——多数同类研究集中于高加索族裔参与者。团队分析了近 1000 名代表新加坡多族裔人口的参与者，比较了无认知障碍者与轻度思维障碍者的状况。亚洲研究尤为关键，因既往研究表明不同族裔的痴呆相关病症存在差异。

“例如，高加索族裔痴呆患者中，阿尔茨海默病主要风险基因载脂蛋白 E4 的流行率约为 50-60%，但新加坡痴呆患者中该比例不足 20%。”坎迪亚副教授同时担任李光前医

学院痴呆研究中心主任，他指出：“因此在高加索患者中得出的研究结论未必适用于亚洲人群，反之亦然。”

预测阿尔茨海默病发生前的病变

大脑血管周围存在称为“血管周围间隙”的空间，β-淀粉样蛋白和 tau 蛋白等阿尔茨海默病患者体内大量存在的有毒废物通过此处排出。若因大脑清除系统效率下降导致这些“排水道”堵塞，就会形成可在 MRI 扫描中观察到的扩大的血管周围间隙。但此前尚不明确该状况是否与痴呆症（特别是阿尔茨海默病）存在关联。

南洋理工大学研究团队通过比对更多阿尔茨海默病指标，解决了早期研究的局限性。他们将堵塞的脑部“排水道”与该病标志性指标——β-淀粉样蛋白和大脑白质损伤（连接脑部各区域的神经纤维网络）进行了对比分析。

研究涵盖新加坡近 1000 名参与者，包括近 350 名无认知问题者（其思维、记忆、推理、决策和专注等认知能力正常）。其余参与者表现出认知疾病的早期特征，包括轻度认知障碍——这是痴呆症显性发作前的阶段。既往研究表明，轻度认知障碍者发展为阿尔茨海默病或血管性痴呆（因脑部血流减少导致的痴呆）的风险更高。

在最新研究中，研究人员分析了参与者的 MRI 扫描结果，发现轻度认知障碍者相比其他参与者更易出现脑部“排水道”堵塞，即扩大的血管周围间隙。科学家还检测了参与者血液中七种特定生化物质（包括 β-淀粉样蛋白和 tau 蛋白），这些物质的存在是阿尔茨海默病的预警信号。

脑部“排水道”堵塞与七项测量指标中的四项显著相关。这意味着扩大的血管周围间隙者更可能伴有大脑中异常增多的淀粉样斑块、tau 蛋白缠结和脑细胞损伤，因此发展为阿尔茨海默病的风险更高。

研究人员还探究了白质损伤（阿尔茨海默病公认的指标）是否与疾病相关生化物质存在关联，结果在七项指标中发现六项相关性，但存在关键差异。当进一步将白质损伤与扩大的血管周围间隙对比时，发现轻度认知障碍参与者中，阿尔茨海默病相关生化物质与扩大的血管周围间隙的关联性比与白质损伤更强。这表明堵塞的脑部“排水道”是阿尔茨海默病的早期指标。

这些发现使临床医生能更准确判断应采用何种治疗方案，在永久性脑损伤发生前及早延缓和预防阿尔茨海默病。“研究具有重大临床意义，”坎迪亚副教授表示，“尽管白质损伤在临床实践中更广泛用于评估痴呆症（因其在 MRI 扫描中易于识别），但我们的

结果表明，扩大的血管周围间隙在检测阿尔茨海默病早期迹象方面可能具有独特价值。”

新加坡邱德拔医院老年医学科高级顾问兼副主任郭真妮（Rachel Cheong Chin Yee）博士评价：“该研究揭示了脑部小血管的变化——本例中即围绕血管并帮助清除脑部废物的扩大的血管周围间隙——可能促成阿尔茨海默病。”未参与该研究的郭博士指出：“这些发现意义重大，因为它们表明显示扩大的血管周围间隙的脑部扫描，或能帮助识别阿尔茨海默病高风险人群，甚至在症状出现前。”

新加坡国立大学医院神经内科顾问张耀丰（Chong Yao Feng）博士（同为新加坡国立大学杨潞龄医学院临床助理教授，未参与研究）表示，脑血管疾病（导致脑血管问题的病症）与阿尔茨海默病传统上被认为由不同机制引发。“该研究发现引人入胜，它证明两种疾病以协同方式相互作用。”张博士解释道，若医生为评估患者认知症状开具脑部 MRI 扫描，发现 NTU 研究中涉及的扩大的血管周围间隙等脑血管疾病标志物，不应仅归因于血管问题——因为这些标志物的存在可能增加患者同时患阿尔茨海默病的风险。“医生需结合患者扫描结果、症状进行临床判断，并与患者讨论是否需进一步检查以确认阿尔茨海默病。”他补充道。

南洋理工大学研究团队计划跟踪研究参与者，统计最终发展为阿尔茨海默病痴呆的人数，以验证扩大的血管周围间隙能否预测这些堵塞“排水道”者更易进展为痴呆。随着更多研究在其他人群建立堵塞“排水道”与阿尔茨海默病的关联，未来脑部 MRI 扫描中检测扩大的血管周围间隙或可加入临床现有工具库，更早确定患者是否会发展为阿尔茨海默病。

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