Neurologic phenotypes associated with COL4A1/2 mutations
Expanding the spectrum of disease

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Study objective
To characterize the neurologic phenotypes associated with COL4A1/2 mutations.

Summary results
COL4A1/2 mutations are associated with a typical severe neurologic presentation and a broad spectrum of milder phenotypes with epilepsy as the predominant feature.

What is known and what this paper adds
COL4A1/2 mutations cause a broad spectrum of cerebrovascular diseases. This study clarifies the neurologic phenotypes associated with these mutations.

Participants and setting
This study analyzed 55 previously reported patients with COL4A1/2 mutations and epilepsy who were identified through a PubMed search. This study also analyzed 44 previously unreported patients with pathogenic COL4A1/2 mutations who were identified through informal links and contact with established consortia. The previously unreported patients lived in Germany, the UK, Italy, Denmark, Australia, the USA, Estonia, Japan, and Portugal.

Design, size, and duration
A customized questionnaire was used to collect clinical and genetic data. Additional clinical data, including seizure history data, were collected for the previously unreported patients. EEG and MRI data were analyzed when available.

Primary outcome measures
The primary outcomes were neurologic presentations.

Main results and the role of chance
The most common phenotype involved childhood-onset focal seizures, with status epilepticus and resistance to antiepileptic drugs being frequent complicating factors. EEG typically revealed focal epileptiform discharges in the context of other abnormalities. Of the previously unreported patients who experienced focal seizures, approximately half had a perileuencephalic cyst or a malformation of cortical development colocalized with the area of the focal epileptiform discharges in brain MRIs, and these patients often exhibited extensive white matter abnormalities as well. This study also identified a subgroup of patients who had epilepsy as their main clinical feature and nonspecific findings in brain MRIs.

Bias, confounding, and other reasons for caution
This study had a relatively small sample size and limited follow-up data.

Generalizability to other populations
This study’s participants were predominantly young, so the generalizability of the results to older patients may be limited.

Study funding/potential competing interests
This study was funded by the EU and by the UK, and Estonian governments, and by various foundations. Some authors report receiving honoraria and research funding/support from various healthcare companies, having an academic collaboration with Congenica, and serving on journal editorial boards. Go to Neurology.org/N for full disclosures.
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Editors’ note: Clinical relevance of acute cerebral microinfarcts in vascular cognitive impairment

In the article "Clinical relevance of acute cerebral microinfarcts in vascular cognitive impairment," Dr. Ferro et al. identified acute cerebral microinfarcts (ACMIs)—defined as supratentorial hyperintensities <5 mm in size on diffusion-weighted imaging (DWI) with 3-Tesla (3 T) MRI—in 16 of 783 patients in a memory clinic cohort of patients with vascular brain injury on MRI. They found that the ACMI presence was associated with a high burden of cerebrovascular disease markers such as lacunar and nonlacunar infarcts, severe white matter hyperintensities, and microbleeds and that these patients were more likely to have the composite outcome of marked cognitive decline, major vascular events, death, and/or institutionalization over a median of 2.1 years of follow-up. In response, Cao et al. highlighted the 48-fold difference in the sample size between the 2 groups with and without ACMIs (noting potential limitations in sensitivity of 3 T MRI), the low occurrence of end points of interest in the ACMIs group, and the shorter median time of the follow-up, as potentially limiting the statistical power of the study. They argue that differences in the other imaging markers between the groups may be a source of confounding and that larger sample sizes with propensity score matching may help validate the study’s findings. They also note that patients with larger DWI-positive lesions should have been excluded to avoid further confounding and that baseline characteristics of the 2 centers in the study should have been compared. Replying to these comments, the authors counter that despite the ACMIs being a rare occurrence, they were statistically significant predictors of multiple end points even when adjusted for other imaging markers, arguing against a substantial power-related limitation. They note that none of the patients with ACMIs had the larger DWI-positive lesions and argue that such lesions had a negligible confounding effect on the results. With the improving sensitivity of research MRI scans, such ACMIs are likely to be detected more often, permitting more granular analyses of this phenomenon in vascular cognitive impairment.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
Neurology® 2020;94:329. doi:10.1212/WNL.0000000000008968

Reader response: Clinical relevance of acute cerebral microinfarcts in vascular cognitive impairment

Shugang Cao (Hefei, China), Yuancheng Li (Nanjing, China), Wen'ian Xu (Hefei, China), and Mingwu Xia (Hefei, China)

We read with interest the article by Ferro et al.¹ that focused on acute cerebral microinfarcts (ACMIs) in vascular cognitive impairment. Although the total sample size was large, a marked difference of approximately 48-fold in the sample size existed between the 2 groups. Given the lower sensitivity of 3T MRI, the low occurrence of end points in the ACMIs group, and the shorter median follow-up time, the study might suffer from low statistical power. Moreover, significant differences existed in imaging markers, and the influences of these factors on prognosis...
and cognitive decline were not well illustrated. Accordingly, it may be more convincing to increase the sample size and use the propensity score matching method to eliminate the influences of these confounding factors.

In addition, the number of patients with the 6 larger DWI-positive lesions and the group they belonged to were not mentioned. Owing to the greater impact of larger infarcts on cognitive function, these patients should be excluded to eliminate the impact of these confounders and statistical discrepancy. Finally, baseline information of the samples from 2 medical centers should be compared to reduce population heterogeneity, which should be demonstrated in the article.


Author response: Clinical relevance of acute cerebral microinfarcts in vascular cognitive impairment

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We thank Cao et al. for their interest in our study. We agree with their comments that acute cerebral microinfarcts (ACMIs) on 3T MRI are a relatively rare occurrence in memory clinic patients. However, the point that we made in our article is that, despite the fact that this MRI phenomenon is quite rare, it may nonetheless be clinically relevant. We showed ACMIs to be statistically significant predictors of multiple endpoints, including stroke, institutionalization, and a composite of poor clinical outcome even when corrected for the presence of other co-occurring imaging markers of vascular brain injury. In fact, low statistical power would rather under- than overestimate such clinical associations.

We fully agree with the authors that diffusion-weighted imaging-positive lesions larger than 5 mm are also of clear interest. Of note, we did not observe these larger diffusion-weighted imaging-positive lesions in any of 16 patients with ACMIs. Considering the large sample of the cohort, their confounding effect on the results is probably negligible. We look forward to future studies on ACMIs, which should preferentially include hundreds of patients—like our cohort—or even thousands, to fully appreciate the clinical relevance of these lesions (also in other cohort types).


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Author disclosures are available upon request (journal@neurology.org).
Reader response: Teaching NeuroImages: Morning glory disc anomaly

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We read with interest the Teaching NeuroImages presentation by Poillon et al.1 The authors provided good ocular fundus and MRIs of a 7-month-old girl presenting with strabismus. The pathology depicted, however, does not correspond to the stated cavitary morning glory optic disc anomaly (MGDA), but instead to that of a peripapillary staphyloma.

Cavitary optic disc anomalies comprise a range of nerve tissue defects, from optic pits to colobomas to MGDA, that generally feature peripheral compensatory bypass cilioretinal vessels in areas of central vasculature and nerve tissue defects.2–5 Owing to an absence of barrier tissue, CSF may also seep from the subarachnoid into the subretinal space leading to retinal detachments.2–5 Peripapillary staphylomas, on the other hand, feature no optic nerve cavitary loss, funnel-shaped or otherwise, but result from a thinned dural sclera surrounding the nerve, permitting a flat-based outpouching of the globe.2–5 Rather than the retinal dysplasia with almost invariably poor vision seen in MGDA, there is stretching of the peripapillary retina with an enlarged blind spot, but vision can otherwise be preserved.2–5

It is important to make such distinctions as peripapillary staphylomas—unlike MGDA—are unassociated with retinal detachments or brain disorders, and neuroimaging is not indicated.3,5

We would like to thank Drs. Karimi and Sanjari for their interest in our case and their very pertinent comments. Distinguishing cavitary optic disc anomalies, such as morning glory optic disc anomaly (MGDA), from peripapillary staphyloma is indeed very relevant because management, prognosis, and follow-up differ between the 2 diagnoses.

In our case, a peripapillary staphyloma was initially included as a differential diagnosis. However, fundoscopy, ultrasound, and MRI under general anesthesia allowed our multidisciplinary team, specialized in pediatric ophthalmology and ophthalmologic imaging, to make a final diagnosis of MGDA. The fundoscopy showed a specific radial aspect of the retinal vessels, whereas retinal vasculature is usually normal in peripapillary staphyloma. Ultrasound and MRI ruled out the diagnosis of peripapillary staphyloma by showing abnormal tissue at the optic nerve insertion consistent with a glial tuft. This diagnosis was confirmed by the French National Center of Reference for MGDA. Moreover, a retinal detachment occurred during the first year of follow-up and was treated by vitrectomy and laser, further confirming the diagnosis of MGDA.

MGDA, whose diagnosis remains based on fundoscopy results, may display various imaging patterns on an MRI, especially regarding its papillary cavitation, suggesting that it might not be a uniform entity.


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In the article “Neurologic phenotypes associated with COL4A1/2 mutations: Expanding the spectrum of disease” by Zagaglia et al., the text for “3/M, 5 years” under the “Mutation Gene” column in supplementary table 3a should read “c.607G>A; p. G203R//paternal.” The authors regret the error.

Reference