Right-to-Left Shunt in CADASIL Patients: A Comorbidity Factor?

To the Editor:

In 2001 Angeli et al.1 reported a remarkably high prevalence of right to left shunt (RLS) in a single CADASIL pedigree, suggesting “a possible association between CADASIL and RLS”. Surprisingly, and notwithstanding the large volume of data building up on CADASIL pathogenesis and diagnosis, no further data has followed this first and only publication on this topic up to now. This is why we read with much interest the article from Zicari et al.2 reporting on a very high prevalence of RLS (71%) in a sample of 21 patients with CADASIL. However, some concerns have to be issued.

The authors stated that “the high prevalence of RLS in CADASIL patients might not be a coincidence but may rather suggest a common genetic origin of CADASIL and the cardiac septal defect”. From a methodological point of view, this hypothesis should be based on the anatomic demonstration of the source of the RLS itself. Contrast enhanced TCD is highly sensitive in RLS detection when compared to transesophageal echocardiography, but it clearly lacks specificity in differentiating intracardiac shunts (namely, patent foramen ovale [PFO]) versus pulmonary ones (pulmonary fistulas).3 Transesophageal echocardiography confirmation of a PFO would have been required to support the above mentioned hypothesis.

Secondly, the lack of information about patients’ genotype makes the interpretation of prevalence data difficult.

Carrying out a study on CADASIL comorbidity factors and genotype-phenotype relations, Mazzucco et al.4 looked at the prevalence of RLS in a group of 16 CADASIL patients, with a range of 8 different Notch3 mutations. By constrast with Zicari’s article, in this CADASIL population a 25% of RLS prevalence was found, rising to 50% when the subgroup of migraineurs with aura was considered. These figures match those expected with aura.5,6 Results from the Mazzucco et al study could be apparently conflicting both with Angeli’s and Zicari’s, but this cannot be worked out as long as Zicari’s population genotype is apparently conflicting both with Angeli’s and Zicari’s, but this cannot be worked out as long as Zicari’s population genotype is unknown. Mazzucco et al suggested a possible relation between specific Notch3 mutations and the presence of RLS due to a PFO. Angeli et al found a very high prevalence of RLS in a single family with an Arg141Cys mutation. Consistent with such observation, in Mazzucco’s study on CADASIL genotype-phenotype relations, the only 2 patients with Arg141Cys mutation were found to have a large, permanent RLS due to a PFO. These data, together with Angeli’s, could suggest a possible mutation-specific interatrial septal abnormality. Obviously, more patients with Arg141Cys mutation are needed to confirm such an interesting hypothesis and it would be worth knowing more about Zicari’s patients’ genotype.

Nevertheless, in both studies the clinical bottom line is the same: RLS is not necessarily linked to CADASIL as a comorbidity factor. In Mazzucco’s study, this can be said because RLS was not found to be over-represented in most of the tested genotype; in Zicari’s, because, notwithstanding the very high prevalence of RLS in the studied sample, neither clinical nor MRI differences between patients with and without RLS could be found.

Disclosures

None.

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