Incidental Discovery of a Dural Arteriovenous Fistula in a Patient with Activated Protein C Resistance

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Summary: A dural arteriovenous fistula was discovered incidentally in a 58-year-old man with activated protein C resistance who underwent routine outpatient cerebral angiography for workup of multiple intracranial aneurysms.

The development of a dural arteriovenous fistula (DAVF) is a well-recognized sequela of dural sinus thrombosis. Among the most common preexisting conditions for development of sinus thrombosis and subsequent fistula formation are trauma, infection with thrombophlebitis (often related to middle ear or mastoid sepsis), severe dehydration, and thrombophilic states (1).

Among the thrombophilic conditions, activated protein C resistance (APCR) has received relatively little attention in the literature in relation to DAVF, despite its being the most common genetic cause of thrombophilia and, therefore, a significant predisposing factor for sinus thrombosis. Although several reports have documented an increased prevalence of APCR in patients with DAVF (2–4), here we present what is to the best of our knowledge the first case of DAVF discovered incidentally in a patient with APCR.

Case Report

A 58-year-old man presented as an outpatient for cerebral angiography. He had initially been referred to another institution for further investigation of his aneurysms by cerebral MR imaging and MR angiography for workup of multiple intracranial aneurysms. During the interview, the patient volunteered a history of APCR (subsequently confirmed on serologic testing for factor V Leiden [FVL]), from which he claimed he had suffered no ill effects; however, his sister, who also has APCR, had a history of deep venous thrombosis and pulmonary thromboembolism.

Knowing that this patient had APCR, we consulted the hematology service for advice regarding prophylactic anticoagulant therapy during conventional angiography. The hematologists advised that no additional measures were necessary over and above our standard practice of administering 5000 IU of heparin intravenously following cannulation of the common femoral artery. After consent was obtained, angiography was performed as usual under systemic heparinization.

Initial selective injection of the right internal carotid artery confirmed the presence of the three aneurysms shown during MR angiography. Because of a small amount of atheroma at the left carotid bulb, it was decided initially to perform a common carotid injection to minimize the risk of embolic complications. This injection revealed a DAVF fed by the left occipital and middle meningeal arteries, confirmed on subsequent selective injection of the left external carotid artery (Fig 1). On the basis of this finding, injection of the right external carotid artery was also performed. This demonstrated further supply to the fistula by the right occipital and middle meningeal arteries. Left vertebral artery injection also disclosed supply to the fistula from its posterior meningeal branches. No supply to the fistula from either internal carotid artery was present. In retrospect, review of the MR imaging and MR angiography findings shows evidence of the fistula, with large external carotid artery branches seen bilaterally and a large venous channel seen running parallel to the distal segment of the superior sagittal sinus (not shown).

Discussion

Protein C is the key element in a vital natural anticoagulant pathway. Protein C is activated by thrombin bound to thrombomodulin on the surface of endothelial cells. When activated, protein C inhibits coagulation by cleaving, and thereby inactivating, coagulation factors Va and VIIIa (5). In hereditary APCR, protein C is activated in the normal fashion, but cleavage of activated clotting factors is either reduced or absent because of mutation(s) in the genes encoding the clotting factors themselves. More than 95% of hereditary cases are due to FVL, in which a single point mutation at position 506 in the gene encoding factor V results in substitution of glutamine for arginine (FVRS506Q) (6). This substitution removes a cleavage site for protein C in the factor V molecule, rendering FVLS506Q resistant to protein C and, therefore, its anticoagulant effects; however, the procoagulant effect of this mutation appears to confer increased risk of venous, but not arterial, thrombosis (5). It is estimated that around 3% of
the world’s population is heterozygous for this muta-
tion (7), which appears to be unique to whites (5).
Inheritance of APCR follows an autosomal domi-
nant pattern. Heterozygotes carry a sevenfold in-
creased lifetime risk of venous thrombosis, whereas
homozygotes have a 20-fold increased risk. It ap-
pears that concomitant procoagulant factors, such
as oral contraception, pregnancy, and coexistent
low-penetration defects such as protein S or C de-
ficiency are additive in terms of the additional risk
conferred on the affected individual (7). In the case
of transient procoagulant factors, such as the pres-
ence of an intravascular foreign body during con-
ventional angiography, our advice from the consult-
ning hematology team was that no special
precautions should be taken over and above our
standard practice of prophylactic heparinization.
On the basis of our discussions with the hematolo-
gists, however, we would certainly advise systemic
heparinization for patients with APCR who are
undergoing conventional angiography in institu-
tions where prophylactic heparinization is not rou-
tine.
It is now widely accepted that cerebral venous sinus
thrombosis is one of the main underlying etiologic
factors in the development of DAVF (1). Sinus
thrombosis has many potential causes, including
trauma, infection, dehydration, and the procoagulant
state associated with pregnancy, the oral contracep-
tive pill (and other drugs), and congenital or acquired
defects in the coagulation pathways. Among the last
factors mentioned, it has now been well established
that APCR is a significant risk factor for development
of dural sinus thrombosis (8, 9). Moreover, a signifi-
cant increase in the prevalence of APCR in patients
with DAVF has been documented in the literature
(2–4). Thus, it seems logical to conclude that patients
with APCR have an initial predisposition to dural
sinus thrombosis, and, therefore, to the pathophysio-
logic sequence which culminates in DAVF.
In our case, the discovery of the patient’s DAVF
was incidental. Although we had knowledge before
angiography that he had APCR, his symptomatology
was sufficiently vague and his mode of referral to our
institution so specific that we had not considered the
potential relevance of performing common carotid or
selective external carotid angiography. Indeed, it
could be argued that the on-table discovery of his
DAVF was somewhat fortuitous: had the presence of
atheroma at his left carotid bulb not prompted us to
perform a common, rather than internal, carotid in-
jection, we may not have recognized the smaller feed-
ers from his vertebral artery until we reported the
study.
Dural sinus thrombosis and DAVF may have a
multitude of presenting symptoms and signs, making
their diagnosis on clinical grounds difficult. In many
cases, these conditions are minimally symptomatic or
even asymptomatic. In some patients, as in our case,
the symptoms may be vague or mimic other condi-
tions such as transient ischemic attack, cervical spon-
dylosis, or middle or inner ear disease (10, 11). In our
case, the patient’s symptoms were not explained by
the aneurysms detected on the basis of MR and MR
angiography findings. This should perhaps have
prompted a more thorough search for cerebral ve-
nous abnormality on the part of the clinician or the
radiologist concerned, although no mention of the
patient’s APCR was made in the MR imaging refer-
ral. It could be argued that at the time of angiography,
armed with the knowledge of his APCR and his un-
usual symptoms, perhaps we should have been look-
ing more actively for a problem such as dural sinus
thrombosis or DAVF. APCR is relatively common
and has confirmed associations with both dural sinus
thrombosis and dural arteriovenous fistulas.

Conclusion
We believe that this case is of significant interest
from two separate standpoints. First, to the best of
our knowledge, it is the only reported case of inci-
dental discovery of DAVF in a patient with APCR
and thus seems to lend further weight to the hypo-
thesis that DAVF is a sequela of dural sinus thrombosis.
Second, it serves as a salutary warning that, when
dealing with patients with APCR, clinicians and radiologists alike should be aware of the association with dural sinus thrombosis and therefore DAVF. This awareness should prompt active investigation for these potentially dangerous conditions when other causes for the patients’ symptoms have not been found.

References