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Genetics and



Posterior Circulation Ischemic Stroke

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Background

Stroke genetics focus on ischemic stroke subtypes

Subtyping focusing on TOAST/CCS

Other subtyping possibilities?

- Anatomical region
- Biochemical variations

Background

Other subtyping possibilities?

Anatomical region

- Gray vs white matter stroke
- Small vessel
-  - Anterior – posterior circulation stroke

Biochemical variations

- Inflammation
- Coagulation
- Metabolic changes

Background

Anterior and posterior circulation ischemic stroke supposedly share pathogenesis and etiology to a large extent

HOWEVER...

These two vascular beds differ in several respects

Background

Phylogenetics:

In humans, posterior circulation develops after the anterior circulation embryologically

Annectation of posterior circulation to the supratentorial brain is a late development

Lasjaunias P, Berenstein A, Brugge KG. *Surgical Neuroangiography*, Springer-Verlag Berlin Heidelberg New York 2001

Background

Vessel innervation:

Anterior circulation arteries richer in sympathetic nerve endings than posterior circulation arteries

Edvinsson L et al. *Autonomic nerves, mast cells, and amine receptors in human brain vessels. A histochemical and pharmacological study.* Brain Res 1976;115:377-393

Edvinsson L et al. *Physiological role of cerebrovascular sympathetic nerves in the autoregulation of cerebral blood flow.* Brain Res 1976;117:519-523

Endothelial functions differ in the two territories

Perko D et al. *Cerebrovascular reactivity to L-arginine in the anterior and posterior cerebral circulation in migraine patients.* Acta Neurol Scand. 2011;124:269-274

Perko D et al. *Differences between cerebrovascular reactivity to L-arginine in the anterior and posterior cerebral circulation.* Cerebrovasc Dis. 2011;31:358-364.

Vasodilation and vasogenic edema more frequent in the posterior circulation

Grossbach AJ et al. *Hypertensive posterior reversible encephalopathy syndrome causing posterior fossa edema and hydrocephalus.* J Clin Neuroscience E pub Oct 11, 2013

Background

Several conditions more common in the posterior circulation:

Posterior Reversible Encephalopathy Syndrome (PRES)

Hinchey J et al. *A reversible posterior leukoencephalopathy syndrome*. NEJM 1996;494-500

Munoz J, et al. *Posterior reversible encephalopathy syndrome: more than meets the eye*. J Clin Oncol 2013;31:e360-363

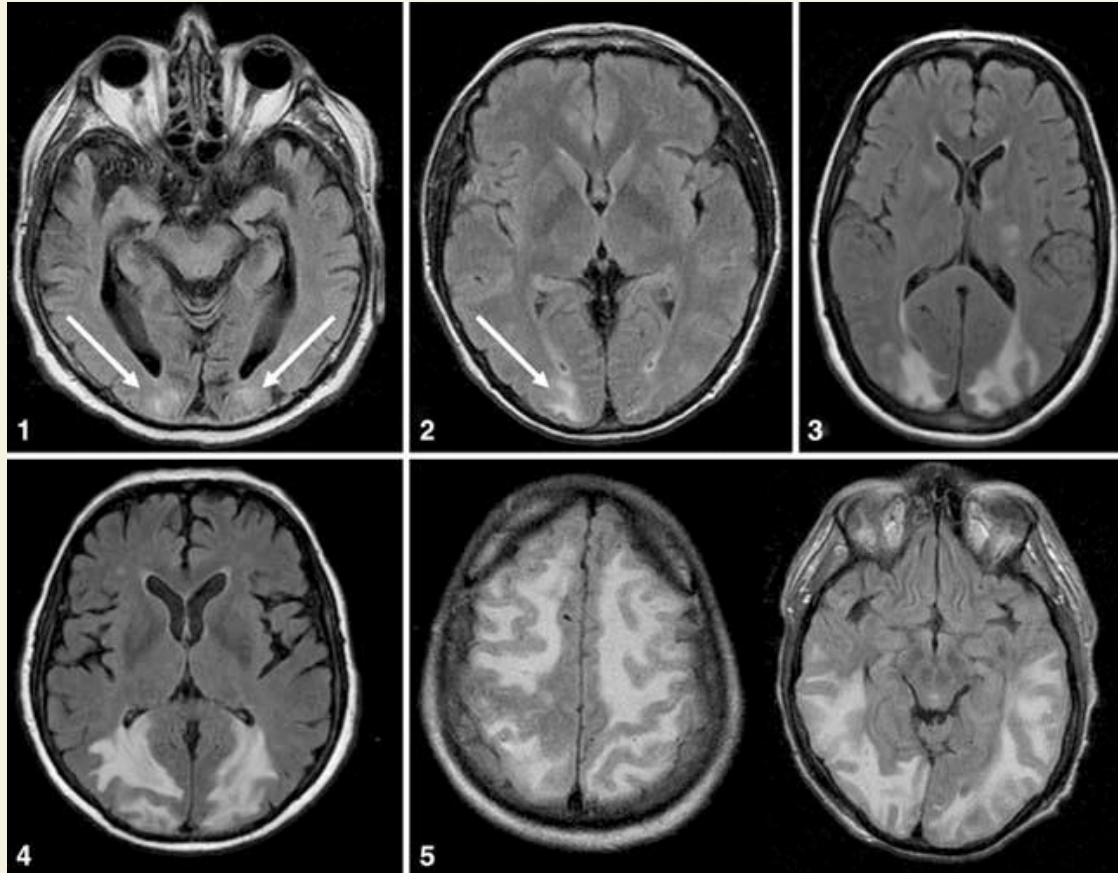
Hypertensive encephalopathy

Grossbach AJ et al. *Hypertensive posterior reversible encephalopathy syndrome causing posterior fossa edema and hydrocephalus*. J Clin Neuroscience E pub Oct 11, 2013

Migraine related ischemic lesions

Kruit MC et al. *Migraine is associated with an increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain iron accumulation: The population-based MRI CAMERA-study*. Cephalalgia 2010;30:129–136

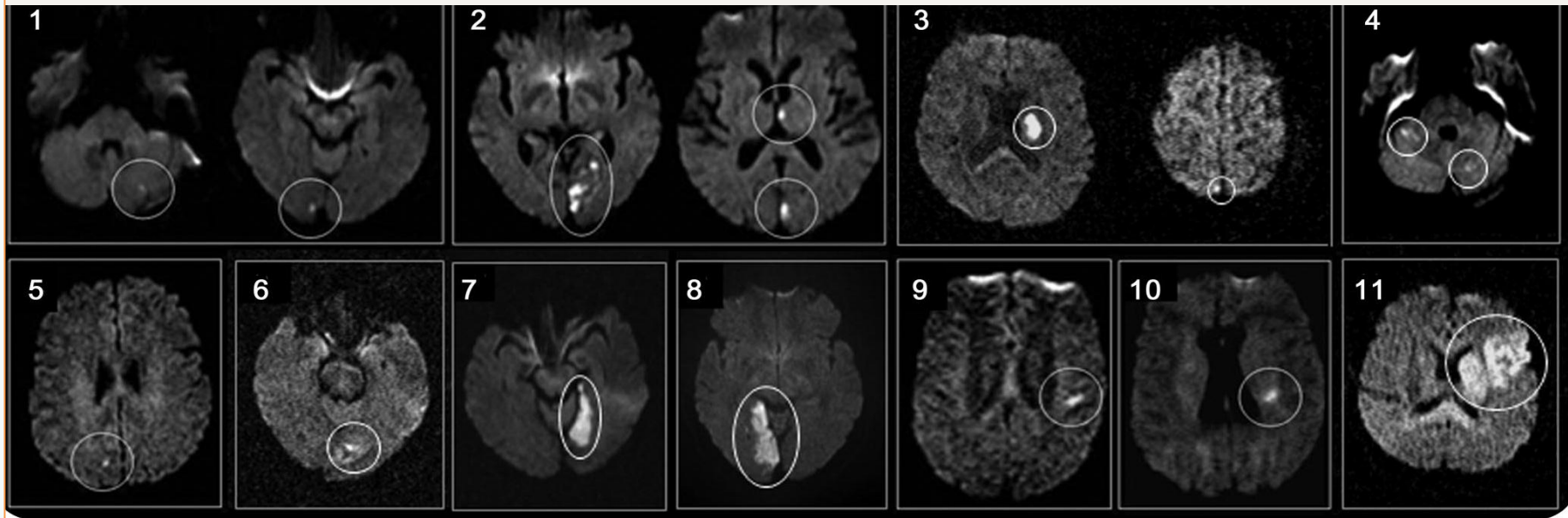
PRES



The clinical and radiological spectrum of posterior reversible encephalopathy syndrome: the retrospective Berlin PRES study.
J Neurol 2012;259:155-164, (p158)

Migraine associated ischemic lesions

predominantly in the posterior circulation territory



Wolf ME, et al. *Clinical and MRI characteristics of acute migrainous infarction*. Neurology, 2011;76:1911-1917

Hypothesis

- Structural and functional differences have impact on:
 - stroke pathogenesis
 - evolution of the acute stroke process
- Specific genetic variations influence risk of ischemic stroke in the posterior circulation

Proposal

Discovery study

Ischemic stroke in the posterior vascular territory

- defined by MRI
- relate to GWAS data

Subjects

- Include patients with PCS
 - Exclude cardioembolic etiology
 - Exclude patients with fetal type PCA?
- Compare with controls without stroke
- If signal – compare with anterior circulation stroke

Subjects

- Subjects from existing SiGN MRI database (if approved) and other databases
- 500-700 subjects excluding CE stroke cases
- Other centers most welcome to participate

Phenotypic Data

Baseline data

- Age, sex, MRI findings, blood pressure, first or recurrent stroke, CCS / TOAST

Vascular risk factors

- Diabetes mellitus, hypertension, smoking, lipid profile, (atrial fibrillation, BMI)

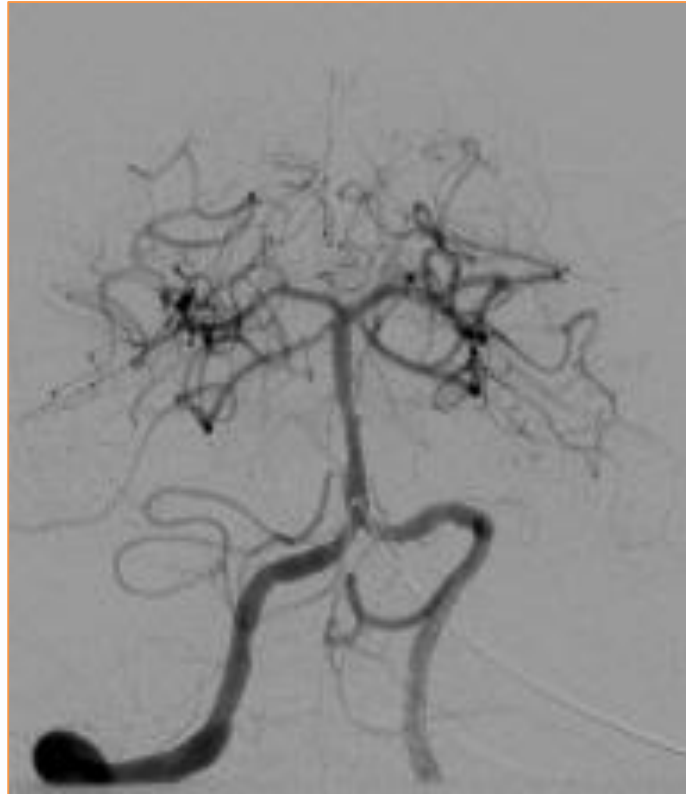
Genotypic Data

- GWA data from participating centers

Conclusion

- New approach to understand genetic risk of ischemic stroke
- Consider pathogenetic subtypes (TOAST/CCS)
- Introduces new phenotypic characterization to shed more light on genetic stroke risk
- Numbers small - probably need to be increased
- Other centers most welcome to participate

Thank you
for your attention



We welcome critical feed-back on this proposal
and
invite you and your center to participate!

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References

Hinchey J et al. *A reversible posterior leukoencephalopathy syndrome*. NEJM 1996;494-500

Munoz J, et al. *Posterior reversible encephalopathy syndrome: more than meets the eye*. J Clin Oncol 2013;31:e360-363

Port JD et al. *Reversible intracerebral pathologic entities mediated by vascular autoregulatory dysfunction*. Radiographics 1998;18:353-367

Grossbach AJ et al. *Hypertensive posterior reversible encephalopathy syndrome causing posterior fossa edema and hydrocephalus*. J Clin Neuroscience E pub Oct 11, 2013

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