

Genetic and epigenetic fundamentals of cerebral vasospasm after aneurysmal subarachnoid hemorrhage

Popular scientific abstract

Introduction: Brain aneurysms are the most common vascular brain pathology and can be appreciated in up to 5% of population. Their burst leads to the most dangerous subtype of stroke. Life-threatening aneurysmal bleeding comprises about 80% of all spontaneous non-traumatic subarachnoid bleeding. Such bleeding can be a devastating incident as 10-15% of patients die instantly at the scene of the event. Those who survive the initial bleeding are at high risk of vasospasm, which is pathological narrowing of the brain artery potentially resulting in inadequate blood supply and neurological deterioration or death. The global and regional socioeconomic burden of this phenomenon is of high importance as most sufferers are under 55 years old, thus still in the working age. Despite the importance, genetic and epigenetic fundamentals remain poorly understood.

Aims: This projects aims to find basic theoretical network relations between human genetic variants, DNA methylation status and in-vivo vasospasm of the main brain arteries in subjects with aneurysmal subarachnoid bleeding.

Study description: Patients admitted with bleeding from brain aneurysm will be scanned for eligibility criteria. Informed consent shall be obtained. As the only surrogate measure of the real in-vivo vasospasm is radiographic vasospasm, ultrasonic diagnosis of vasospasm will be made by means of transcranial Doppler (TCD). Once their aneurysm is repaired and secured, serial monitoring of brain arteries will be done by non-invasive transcranial Doppler (TCD) ultrasonography. Based on their TCD results, subjects will be allocated to one of two groups: A - those with vasospasm; or B – those without vasospasm. 10ml of patients' blood samples will be collected once between days 1 to 4 in order to isolate gDNA, which will be further used for genetic and epigenetic analysis. Genome-wide single nucleotide polymorphism (SNP) genotyping and genome-wide DNA methylation profiling shall be done to identify which relevant SNPs and methylation of which genes take part in vasospasm. Data from SNP genotyping and methylation profiling will be combined to obtain unique methylation quantitative trait loci. Each SNP-methylation pair will be tested for significance.

Rationale for the study: Molecular foundations of the brain vasospasm after aneurysmal subarachnoid bleeding remain unknown. So far, the research focused mostly on the relations between clinical symptoms of vasospasm and genetics. A very small number of studies (and utter lack of European works) touched upon the real in-vivo vascular constriction in the genetic and none in epigenetic setting. Furthermore, analysis mQTL is an undiscovered area for aSAH and vasospasm, which possibly could provide invaluable knowledge for the molecular understanding of the vasospasm As the only surrogate measure of real in-vivo vasospasm is radiographic vasospasm, evaluation by means of transcranial Doppler is chosen since (as opposed to angiography) it is non-invasive, uses clinically safe ultrasounds, and it was proven to be a suitable intermediate measure for genetic association studies

Significance of the results: First, it will deepen the knowledge regarding relations between SNPs and cerebral ultrasonographic vasospasm, especially in the European population, in which it is still utterly unknown. Furthermore, DNA methylation profiling will provide relevant epigenetic background for the altered blood flow in cerebral arteries in patients with aSAH. The study will help understand which genes are hypermethylated or hypomethylated in those with the ultrasonographic vasospasm. These newly acquired fundamentals will be combined to detect mQTLs that are no man's land in the aSAH and that could provide important unprecedented cues to which gene variants affect DNA methylation in the subjects with vasospasm. Knowledge gathered in this basic research could help design future studies aiming to implement it for more practical bioengineering and biotargeting purposes attempting to prevent or treat the vasospasm.