Influence of Haptoglobin on haemorrhage volume and oedema extension distance after intracerebral haemorrhage

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Background

After an intracerebral haemorrhage (ICH) the brain is exposed to extracellular haemoglobin and its toxic breakdown products haem and iron. Haptoglobin (Hp) is an acute-phase protein involved in neutralizing haemoglobin. Hp expression level is influenced by the Hp copy number variant (CNV) (Hp1 versus Hp2), and the rs2000999 single nucleotide polymorphism (SNP). Hp1-1 has previously been associated with better outcomes after ICH.

We investigated the effect of these genetic variations on perihematomal oedema (PHO), a potential mediator of effects on outcome, measured by oedema expansion distance (OED; potential marker of inflammation and haemoglobin toxicity).

Methodology

We enrolled patients from the ICH arm of the CROMIS-2 study, a prospective observational study. Hp CNV was determined by two methods: quantitative polymerase chain reaction (PCR) and conventional PCR.

Hp SNP was determined using Kompetitive Allele-Specific PCR. Measurement of PHE volume on acute CT scan (within three days) was performed via semi-automated, threshold based approach.

Results

We included 738 included patients from the CROMIS-2 study with available blood samples. 317 were female (42.95%) and mean age was 73.3 (SD 12.4). Mean ICH volume was 13.48 (SD 18.36) and mean OED volume was 0.51 (standard deviation 0.23). The distribution of the ICH location was as follows: 301 were lobar (41.23%), 365 deep (50%), 22 in the brainstem (3%) and 42 in the cerebellum (5.75%).

Hp CNV was 122 Hp1-1 (16.55%), 364 Hp2-1 (49.39%) and 244 Hp2-2 (34.06%).

Figure 1: Hp CNV

Hp CNV	
Hp 1-1	122 (16.55%)
Hp 2-1	364 (49.39%)
Hp 2-2	251 (34.06%)

Distribution of the Hp SNP genotype was: 23 A:A (3.22%), 235 A:G (32.87) and 457 G:G (63.92%).

Figure 2: Hp SNP

Hp genotype	
A:A	23 (3.22%)
A:G	235 (32.87)
G:G	457 (63.92)

Neither HP CNV nor SNP genotype was associated with OED in either univariable or multivariable linear regression analysis that included systolic blood pressure, antihypertensive medication, anticoagulation, time to CT, ICH volume and location.

Figure 3: Final multivariable logistic regression model

Variables	Coefficient	95% CI	P value
SBP	0.0003	-0.0003-0.0008	0.36
OAC	0.02	-0.04-0.07	0.55
Time Event to CT			0.13
- Day 1 (reference)			
- Day 2	0.07	0.002-0.13	
- Day 3	0.02	-0.08-0.12	
Cr ICH volume	0.04	0.02-0.06	<0.001
ICH location			<0.001
- cerebellar (reference)			
- Brainstem	-0.04	-0.16-0.07	
- Deep	0.17	0.09-0.24	
- Lobar	0.23	0.15-0.3	
Antihypertensive medication	-0.07	-0.12-(-0.01)	0.01
Hp genotype			0.44
- Hp1-1 (reference)			
- Hp2-1	-0.02	-0.07-0.02	
- Hp2-2	-0.03	-0.08-0.02	
Rs2000999			0.28
- A:A (reference)			
- A:G	0.003	-0.09-0.1	
- G:G	-0.03	-0.12-0.07	

Conclusion

We found no association of either Hp CNV or SNP with acute PHO: If haptoglobin genetic variant influence outcome, it is likely mediated by mechanisms other than through reducing acute PHO.