Metabolites and macromolecules in spinocerebellar ataxias (SCA)- measured by 1H MRS

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Synopsis

Spino-cerebellar ataxia (SCA) is a trinucleotid repeat disease. The gene products contain an increased number of glutamine residues. The purpose of the study was to investigate, whether glutamine and glutamate (Glx) were elevated in SCA, and whether pathological proteins containing Glx were spectroscopically visible as altered macromolecular resonances. In twelve patients and 16 controls, 1H MRS did not reveal elevated macromolecules and free Glx. Correlations between the CAG repeats and the metabolite or macromolecular levels were not present. Inositol was increased in pons, and creatine in cerebellum, where NAA was reduced. This is the first study reporting an elevated Cr in the cerebellum in SCA.

Introduction

Spino-cerebellar ataxias (SCA) are autosomal dominantly inherited cerebellar ataxias characterised by progressive ataxia that results from degeneration of the cerebellum and pons. The mutations in SCA-1,-2, and -3 have been shown to be unstable repeat expansions of Cytosine Adenosine Guanine (CAG). The expanded CAG repeat is translated into an elongated polyglutamine tract within coding regions of the respective genes (1). As the expanded polyglutamine tract is unstable, smaller cleaved proteins and free Glx may contribute to the Glx resonance in 1H MRS. Free Glx is spectroscopically detectable at 2.1–2.5 ppm and 3.6-3.8 ppm. Protein bound Glx is assigned in the macromolecular region of 2.05 and 2.29 ppm (2). Thus, the purpose of this study was to determine, whether free Glx and macromolecular bound glutamine were elevated in SCA patients compared to healthy controls, and whether there was a connection between the genetics and the concentration of Glx.

Methods

Twelve patients with SCA (5 with SCA-1, 5 with SCA-2, 2 with SCA-3, age range 29-62 years, 7males, 5 females) from 11 separate kinships and 16 controls (age range 27-62 years, 10 males, 6 females) were investigated. Spectra were recorded from volumes in the pons and in the left cerebellum. A STEAM sequence (TR/TE 3000/15ms, 6–8 ml, 64 acquisitions) without and with metabolite nulling was applied. Absolute concentrations of macromolecules and Ino, Cho, Cr, Glx and NAA were calculated by an extended LCModel (3). Voxel segmentation into grey and white matter and CSF was performed on T1 weighted images by using spm99, and correction for the amount of CSF within the spectroscopic voxel was performed. Statistical testing including a Bonferroni correction for multiple testing was performed.

Results

Pontine spectra could only be acquired in 11 patients, because in one female patient with SCA-2 no proper shimming of the pontine voxel was possible. Cerebellar spectra could be obtained in all patients with sufficient quality. In pons, only Ino was elevated in patients ($p<0.02$). In cerebellum, NA was reduced ($p<0.005$) and Cr was elevated ($p<0.04$). Correlations between the numbers of CAG repeats and metabolites and macromolecules stratified for anatomic region and SCA type were not found.

Discussion

Differences to the work of Guerrini et al. (4) with a normal NAA in pons in our study are probably attributed to the correction for the csf amount in the VOI. The normal NAA would be consistent with the findings of Verbeek et al. (6) who showed no neuronal loss in the pontine nuclei. CSF correction also allows to find an elevated Ins in Pons and an elevated Cr in cerebellum, which would have been missed without volume correction. The increased Ins might be correlated with astrocytic gliosis. The source of elevated Cr might derive from a Purkinje cell degeneration (6) in the cerebellar foliae leading to a relative majority of granular cells known as to be rich in Cr (7). The length of the tripnucleotid repeat did not directly influence the spectral findings.

References

(1) Martin JB NEJM 1999,340:1970-80. (2) Behar KL et al. MRM 1993,30:38-44. (3) Seeger U et al. MRM 2003,49,19-28.
(4) Guerrini L et al. 2004,127:1785-95. (6) Verbeek DS et al. Brain 2004,127:2551-7. (7) Kaldis P at al. Dev NeuroSci 1996,36:72-7.

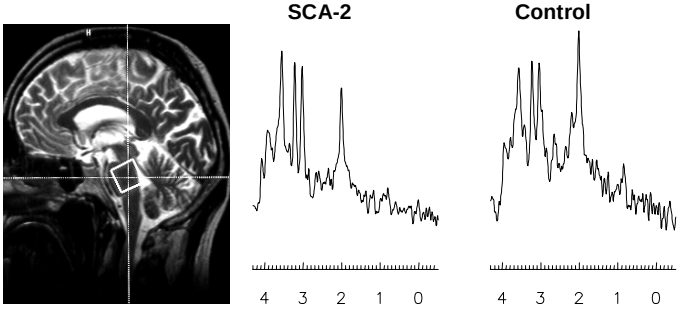

Figure 1 : Pontine spectra of SCA-2 and a control. NAA seems to be reduced according to the increased partial volume of CSF in patients. Ins is elevated.

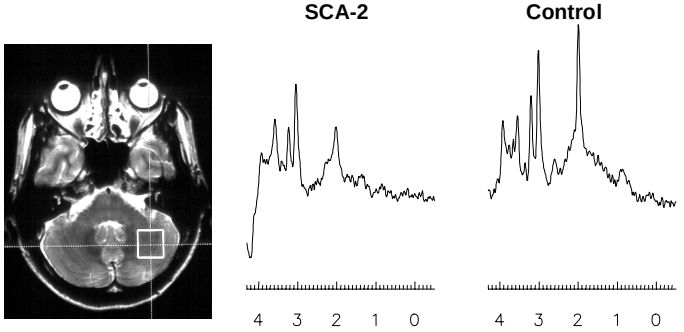

Figure 2: Cerebellar spectra of SCA-2 and a control. After correction for CSF in the VOI Cr is elevated and NAA reduced.

	Cr	Ins	NA	Cho	Glx	lipmm1	mm2	mm3	mm4
Pons SCA	4,38	5,89*	5,62	1,47	4,49	4,18	3,31	4,66	1,30
	(3.37 - 5.31)	(4.34-7.61)	(4,87-6,40)	(1,29-1,61)	(2,02-6,42)	(2,19-4,99)	(1,48-5,32)	(3,04-5,01)	(,79-1,50)
Pons Controls	4,09	3,66*	7,34	1,56	6,66	4,33	5,10	4,69	0,86
	(3.94 - 4.73	(2,82-4,55)	(6,81- 8,00)	(1,48-1,81)	(5,18-9,35)	(3,56-5,29)	(3,46-5,93)	(4,35-5,52)	(0,70-1,14)
Cereb. SCA	7,39*	4,62	5,50**	1,42	8,99	4,12	8,63	7,72	1,61
	(6,53-8,08)	(3,90-5,98)	(4,93-6,55)	(1,20-1,66)	(6,73-11,00)	(2,94-5,93)	(5,73-9,58)	(6,17-9,61)	(1,34-1,89)
Cereb. Contr.	6,86*	4,65	7,72**	1,66	8,52	5,73	9,37	7,26	1,44
	(6,2-7,14)	(3,95-5,53)	(7,39-8,14)	(1,55-1,80)	(7,15-11,49)	(4,70-6,69)	(8,12-10,56)	(6,96-8,12)	(1,26-1,80)

Table 1: Absoute concentrations of metabolites [in mMol/l] and macromolecules [MR visible protons] given as median (95%confidence interval) * $p<0.05$, ** $p<0.005$