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Association between caffeine intake and age at onset in Huntington's disease

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ABSTRACT

Habitual consumption of caffeine, a non-selective adenosine receptor (AR) antagonist, has been suggested to be beneficial in Parkinson's and Alzheimer's diseases. Experimental evidence support that ARs play a role in Huntington's disease (HD) raising the hypothesis that caffeine may be a life-style modifier in HD. To determine a possible relationship between caffeine consumption and age at onset (AAO) in HD, we retrospectively assessed caffeine consumption in 80 HD patients using a dietary survey and determined relationship with AAO. Following adjustment for gender, smoking status and CAG repeat length, caffeine consumption greater than 190 mg/day was significantly associated with an earlier AAO. These data support an association between habitual caffeine intake and AAO in HD patients, but further studies are warranted to understand the link between these variables.

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Introduction

Huntington's disease (HD) is an inherited neurodegenerative disease caused by expanded CAG repeats (>35) in *IT15* gene, characterized by motor, cognitive and psychiatric disturbances (Walker, 2007). CAG repeat length accounts for about 60% of age at onset (AAO) variance while remaining 40% are ascribed to additional genetic and/or environmental factors (Ross and Tabrizi, 2011).

Epidemiological data support that caffeine intake reduces the risk of Parkinson's and Alzheimer's diseases (Chen and Chern, 2011). Caffeine essentially acts as a non-selective AR antagonist (Chen and Chern, 2011). Compelling evidence support the role of A_1 and A_{2A} receptor modulation on motor symptoms and/or neurodegeneration in HD models (Blum et al., 2012 and references herein), raising the hypothesis that caffeine may exert an impact in HD. Thus, this study aimed at evaluating potential association between caffeine intake and AAO or functional/motor decline in a cohort of 80 HD patients.

Methods

Data were retrospectively collected over a two-year period from 8 French sites. The study was approved by Lille University Hospital Institutional Review Board, CCTIRS (no. 08.220) and CNIL (no. 908339). Written informed consent was obtained from all patients. Inclusion criteria were: CAG repeats >35; motor UHDRS (United Huntington's Disease Rating Scale) score ≥5; disease onset *within* the previous ten years; and 2 comprehensive assessments at interval of at least one year. Patients with unreliable information or previous brain surgery were excluded.

Data collection

Demographic variables, AAO, CAG repeat length and scores from the UHDRS: motor score (worst: 124; best: 0), chorea subscore (worst: 28; best: 0), Independence Scale (IS, worst: 0; best: 100) and Total Functional Capacity (TFC, worst: 0; best: 13) were collected. Annual progression of each score was calculated from the 2 assessments. After examination of the patient and caregiver, the date of onset of first symptoms defined the AAO.

Usual caffeine intake over the last ten years was assessed by a validated self-survey filled-in at home by the patient and caregiver. Its reliability, assessed by retest (mean interval: 37.5 ± 5.5 days) in 31 patients, was excellent (intraclass correlation coefficient by Fleiss method: 0.97 [95% CI: 0.94–0.98]). The mean daily intake of caffeine containing items (coffee, tea, chocolate, sodas) was reported, along with any changes of consumption over the 10 year period. All data were then confirmed by telephone interview with the caregiver, by the same neurologist, to withdraw unreliable data. Mean caffeine intake *before* then *after* disease onset was calculated. Cigarette smoking was expressed in pack/year, and any consumption changes were considered. Alcohol consumption was evaluated by a binary semi-quantitative scale ("rare or never" vs. "weekly or daily").

Statistical analysis

All statistical analysis was performed using SAS software V.9.2. Continuous data are expressed as mean with standard deviation. Qualitative data are expressed as frequency and percentage. P-values <0.05 were considered significant. Two groups of caffeine consumers were defined by dichotomizing caffeine intake *before* disease onset according to its median ("high" consumers: ≥ median; "low" consumers: < median). The normality of distribution was assessed by the Shapiro–Wilk test. Comparisons between these two groups were executed with a Student *t*-test for continuous data and with a Chi-square test or a Fischer Exact test for qualitative variables. The relationship between AAO and CAG repeat number was assessed by a linear regression. To identify the other factors linked to AAO, we performed linear regressions adjusted on CAG repeat. Variables with a significant level <0.2 were introduced into a multivariable linear regression. The linear model assumptions were checked using the studentized residuals and the individual's influence was assessed with the Cook's distance. A sensitivity analysis was performed by removing the subjects having caffeine intake >90th percentile. Functional and motor decline was compared between the two groups by covariance analysis to adjust results on the baseline and CAG repeat number.

Results

Demographic characteristics (Table 1) were comparable with other studies (Marder et al., 2000). Caffeine intake before disease was correlated with tobacco consumption in pack/year ($r = 0.37$, $p = 0.0007$). Linear regression analysis indicated that CAG repeat length explained 59% of AAO variance ($p < 0.0001$). Average caffeine intakes before and after disease onset were strongly correlated ($r = 0.88$; $p < 0.001$). There was no significant link between motor UHDRS and caffeine intake when adjusted on disease duration, smoking and gender ($p = 0.21$). Median caffeine consumption before onset was 190 mg/day (~2 small cups of regular coffee), which determined the 2 caffeine consumer groups (< and ≥ to 190 mg/day) without any significant difference in demographic characteristics (Table 1). Time elapsed between disease onset and consumption assessment was similar for both groups (<190 mg/d: 6.85 (2.24); ≥190 mg/d: 6.15 (2.45) years; $p = 0.19$). In bivariate analysis adjusted to CAG repeat length, earlier AAO was associated with higher caffeine consumption before disease onset (≥190 mg/day) (−4.7 (1.6) years; $p = 0.0041$), smoking (pack/year) (−0.2 (0.1); $p = 0.0049$) and female gender (−3.7 (1.6) years; $p = 0.0266$). CAG length on the normal allele ($p = 0.7511$) and alcohol consumption ($p = 0.3829$) did not influence AAO. In the multivariable linear regression model, higher caffeine consumption before disease onset (≥190 mg/day) remained significantly, although less strongly, associated with earlier AAO (−3.6 (1.6) years; $p = 0.0270$). No significant associations were observed between smoking ($p = 0.0710$) or gender ($p = 0.0827$) and AAO. Results were similar after removing subjects with caffeine intake >90th percentile (i.e. >790 mg/day). Finally, no significant difference was observed between the two groups for decline of IS ($p = 0.1564$), TFC ($p = 0.1716$), total motor UHDRS score ($p = 0.233$) and chorea subscore ($p = 0.944$).

Discussion

Our study supports a link between caffeine consumption and AAO in HD, with consumption greater than 190 mg/day associated with earlier AAO. This AAO difference reached about 4 years in multivariate analysis. This is thus far from negligible as in average HD patient life-span is 15–20 years (Walker, 2007). This study is among the rare ones reporting an association between an environmental factor and HD, here concerning with the most consumed psychoactive substance in the world.

Caffeine has several pharmacological targets that potentially underlie its actions: adenosine receptors, phosphodiesterases or ryanodine receptors (Fredholm et al., 1999). While modulation of phosphodiesterases or activation of ryanodine receptors – leading to modified calcium dynamics into neurons – could play a role (Giralt et al., 2011; Suzuki et al., 2012), concentrations of caffeine needed to act on these targets are difficult to reach in the frame of a nontoxic consumption. Plasma concentrations achieved in the frame of habitual caffeine intake are essentially compatible with adenosine receptor inhibition (Chen and Chern, 2011; Chen et al., 2010; Fredholm et al., 1999).

Caffeine share similar affinity for both A_1 and A_{2A} receptors but following chronic consumption, at least from the psychomotor point-of-view, tolerance develops and involves A_1 but not A_{2A} receptors

Table 1
Demographic characteristics of the study population and distribution according to median caffeine intake (190 mg/day). AAO, Age at Onset; IS, Independence Scale; TFC, Total Functional Capacity; UHDRS, Unified Huntington's Disease Rating Scale.

	All patients	Patients with caffeine intake <190 mg/d before disease onset	Patients with caffeine intake ≥190 mg/d before disease onset	p-Value
Gender (M/F) n	41/39	18/22	23/17	0.2634
AAO (y): mean (SD)	47.4 (11.5)	49.5 (12.7)	45.4 (10.0)	0.1144
Disease duration (y): mean (SD)	6.5 (2.4)	6.8 (2.2)	6.2 (2.4)	0.1874
CAG (longer allele): mean (SD)	44.1 (3.4)	44.2 (3.4)	44.0 (2.6)	0.7680
CAG (smaller allele): mean (SD)	19.5 (4.1)	20.4 (4.6)	18.7 (3.5)	0.0666
Mean daily caffeine intake before AAO (mg/day): mean (SD)	315.0 (435.8)	80.8 (64.6)	549.3 (517.7)	<0.0001
Mean daily caffeine intake after AAO (mg/day): mean (SD)	294.4 (346.1)	122.9 (181.4)	466.0 (386.4)	<0.0001
Smoking (pack/year): mean (SD)	9.4 (14.1)	5.3 (10.6)	13.7 (16.0)	0.0080
Annual IS decline: mean (SD)	−3.5 (7.1)	−4.9 (7.1)	−2.1 (6.9)	0.1072
Annual TFC decline: mean (SD)	−1.0 (1.4)	−1.1 (1.4)	−0.8 (1.4)	0.3778
Annual motor UHDRS decline: mean (SD)	+5.5 (8.4)	+7.1 (8.9)	+3.7 (7.6)	0.1028
Annual chorea (UHDRS subscore) impairment (SD)	+1.3 (4.1)	+1.6 (4.5)	+1.1 (3.6)	0.6426

(Potenza et al., 2013 and references herein) suggesting that effects of chronic caffeine intake is likely related to A_{2A} receptor blockade. Interestingly, previous findings support that detrimental effect of caffeine could be ascribed to A_{2A} receptor blockade as high doses of A_{2A} receptor antagonists and global knockout of A_{2A} receptors have been shown to worsen HD models (Blum et al., 2003a, 2003b; Mievis et al., 2011) while A_{2A} receptor activation was found beneficial (Chou et al., 2005; Huang et al., 2011). This is also in accordance with a pioneer work showing that mutated Huntingtin leads to A_{2A}R hyper-sensitivity and abnormal transduction, reversed by antagonist treatment (Varani et al., 2001). Underlying molecular mechanisms remain unclear but this could, among others, involve post-synaptic dysregulations of striato-pallidal neurons (see Blum et al., 2003a, 2003b, 2012 for reviews and discussion). A_{2A} receptor blockade by caffeine could also lead to a detrimental impairment of Brain-derived Neurotrophin Factor-related release and signaling (see Blum et al., 2003a, 2003b, 2012; Tebano et al., 2010 for reviews and discussion). However, this would deserve specific studies as other data point out that caffeine could prevent BDNF loss during aging (Sallaberry et al., 2013) and that coffee fruit extracts significantly increase plasma BDNF levels in humans (Reyes-Izquierdo et al., 2013). We cannot firmly rule out that caffeine effect in HD is mediated through A_1 receptors. Indeed, we previously described that A_1 receptor activation was associated with a protective effect in a rat model of HD by reducing excitotoxicity (Blum et al., 2002). Contribution of A_1 receptors to HD physiopathology remains to be however further evaluated in transgenic models.

Finally, there are other possible explanations and several limitations in our study, performed in a first attempt towards a larger prospective evaluation. First, the retrospective recall of caffeine intake could lead to inaccurate data collection. Second, it could be suggested that caffeine may have an enhancing role towards motor function. In this case, difference in caffeine consumption would change the onset but not necessarily the pathological process. However, we found no correlation between caffeine intake and motor score. Third, prodromal/early behavioral features like obsessive or compulsive disorders, sleep or circadian cycle modification may have altered caffeine habit. So, behavioral features should be closely examined in a further study. Finally, genetic determinants may cause both an earlier onset and a higher caffeine intake. Indeed it has been shown that some variants in ADORA2A or CYP1A genes, the main caffeine metabolizing enzyme, influence caffeine consumption or its behavioral effects (Rogers et al., 2010; Sulem et al., 2011), and also that a variant in ADORA2A is associated with AAO (Dhaenens et al., 2009; Taherzadeh-Fard et al., 2010).

In conclusion, present data support a link between caffeine intake and AAO in HD. However, neither causation relationship nor life-style advice can be inferred from our data. Prospective studies are warranted to explore this link and all possible related factors as highlighted in this preliminary study.

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