Cerebrospinal fluid endocannabinoid levels in Gilles de la Tourette syndrome

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Gilles de la Tourette syndrome (TS) is a complex neurodevelopmental disorder characterized by the presence of motor and vocal tics as well as psychiatric comorbidities such as attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), depression, and anxiety. The underlying cause of the disease is still unknown, but several lines of evidence suggest a paramount role of the dopaminergic system. Based on the clinical observation that cannabis-based medicine including cannabis and delta-9-tetrahydrocannabinol (THC, dronabinol) may improve TS, alternatively, an involvement of the endocannabinoid system (ECS) has been suggested. In this study we measured cerebrospinal fluid (CSF) levels of the two most important endocannabinoids "N"-arachidonoyylethanolamine (AEA, anandamide) and 2-arachidonoylglycerol (2-AG), the endocannabinoid-like molecule palmitoyl ethanolamide (PEA), and the lipid arachidonic acid (AA) in a sample of adult patients with TS (n = 20) compared with controls (n = 19) using liquid-liquid lipid extraction and simultaneous quantification by liquid chromatography multiple reaction monitoring (LC/MRM). CSF levels of AEA (p = 0.0018), 2-AG (p = 0.0003), PEA (p = 0.02), and AA (p < 0.0001) were significantly increased in TS compared with controls. Levels of 2-AG correlated with the severity of comorbid ADHD (p < 0.01). This is the first study, demonstrating alterations in the ECS suggesting an involvement of this system in the pathophysiology of TS. It can be speculated that elevated endocannabinoid levels either represent secondary changes in order to compensate for alterations in other neurotransmitter systems such as the dopaminergic system, are simply an epiphenomenon or, alternatively, represent the primary cause of TS.
approved by the local ethics committee (no. 6987) at Hannover Medical School.

In all patients, extensive clinical assessments were performed at the day of lumbar puncture to assess severity of both tics and psychiatric comorbidities by using the following established clinical assessments: Yale Global Tic Severity Scale—Total Tic Score (YGTSS-TTS) [13], Premonitory Urge for Tics Scale (PUTS) [14], Gilles de la Tourette-Syndrome Quality of Life Scale (GTS-QOL) [15], Beck Depression Inventory-II (BDI-II) [16], Conner’s Adult ADHD Rating Scale (CAARS) [17], DSM-IV symptom list for ADHD [18], Wender Utah Rating Scale short version (WURS-K) [19], Beck Anxiety Inventory (BAI) [20], Yale–Brown Obsessive Compulsive Scale (Y-BOCS) [21], and Brief Symptom Inventory (BSI) [22].

In parallel, a control group (n = 20, 13 females, mean age = 45 (±20 SD, range, 18–79 years)) was recruited (between 03/2017 and 09/2017) at the Department of Neurology at Hannover Medical School. The control group consisted of patients suffering from either normal pressure hydrocephalus (NPH) or idiopathic intracranial hypertension (IIH) (diagnoses were confirmed by one of the authors (KWS)), who received lumbar puncture for therapeutic reasons. Hence we decided to include only patients with these diagnoses to control disease related CSF changes the control group could not exactly be age or sex matched. None of the controls was treated with cannabis-based medicines or used cannabis recreationally, but six patients with IIH received treatment with acetazolamide.

Lumbar puncture and routine CSF analyses

Lumbar puncture was performed in all subjects in a sitting position at the same daytime (patients with TS: between 12.00 p.m. and 3.10 p.m., controls: between 10 a.m. and 2 p.m.). In patients with TS, all lumbar punctures were done by one of the authors (KWS). All subjects were in a non-fasting status. All CSF samples were frozen at −80 °C within 20 (TS) and 60 (controls) minutes, respectively, and were not thawed before shipment to Mainz for further analyses. To exclude a significant influence of different freezing times, the effect of different freezing times on endocannabinoid concentrations was assessed in a separate experiment (see supplementary Fig. 1). In all TS patients, in addition, routine parameters were assessed including CSF cell count, cytology, blood-CSF barrier function by CSF-serum albumin quotients (QAlb), and oligoclonal bands (OCB) (for further details see [12]).

Measurement of endocannabinoid levels

All samples were measured at the Lipidomics/Mass Spectrometry Facility at the Institute for Physiological Chemistry at the University Medical Center Mainz. Endocannabinoids were extracted from 500 µL CSF using a previously reported liquid-liquid extraction [11, 23, 24] which was adapted to the specific CSF volume, i.e., 500 µL. Briefly, frozen CSF was allowed first to thaw on ice (4 °C). 500 µL of ethylacetate/n-hexane (9:1, v/v) containing deuterated internal standards of the endocannabinoids, arachidonic acid and endocannabinoid-like lipids (PEA and oleoylethanolamide (OEA)). The resulting mixture was vortexed for 30 s and centrifuged for 10 min at 20000 g at 4 °C resulting in two-phase separation. The hence resulting mixture was allowed to freeze at −20 °C for 10 min, the upper organic phase was recovered and evaporated to dryness under a stream of nitrogen. The dry lipid extracted was solubilized in 50 µL acetonitrile/water from which 10 µL were injected into liquid chromatography/multiple reaction monitoring (LC/MRM) instrument. The LC/HRMS analytical conditions and parameters for qualitative and quantitative analysis were as described elsewhere [11, 23–25]. The endocannabinoid levels determined by LC/HRMS were normalized to the CSF volume. Levels of AEA, 2-AG, PEA, and AA— from which both endocannabinoids are derived and/or produced— were measured.

Measurement of exocannabinoids

Serum levels of THC and its metabolites 11-hydroxy-THC (THC-OH) and 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH) were measured in all subjects (patients and controls) at the Forensic Toxicological Centre Munich to assess levels of exocannabinoids. The procedure used—liquid/liquid extraction followed by LC/HRMS— is accredited under DIN EN ISO 17025 with the following limits of detection (LOD) and quantitation (LOQ): 0.05 ng/ml and 0.20 ng/ml for THC, 0.03 ng/ml and 0.12 ng/ml for THC-OH and 0.76 ng/ml and 2.62 ng/ml for THC-COOH, respectively.

Statistical analyzes

All statistics were calculated using SPSS and Graph Pad Prism 7.03. For statistical analysis a p value < 0.05 was considered significant. All statistical analyses were performed using two-tailed testing. As all dependent variables were normally distributed tested using Kolmogorov–Smirnow test, parametric tests were used throughout. Due to the small sample sizes, we assumed variance homogeneity for all tests. For multiple comparisons Bonferroni correction was used.

Data availability statement

Any anonymized data not published within this or a related [12] article will be shared by request from any qualified investigator.

RESULTS

In this study, we included adult patients with TS (n = 20, 2 females, mean age = 36.1 (±14.34 SD, range, 19–64 years), mean age at tic onset = 7.7 years (±2.8 SD, range, 3–13 years), and mean tic severity (YGTSS-TTS) = 23.2 (±9.1 SD, range, 10–39)). For further clinical details see Table 1 and [12]. Seventeen patients were unmedicated, one patient received medication for tics with aripiprazole, and two patients reported treatment with cannabis-based medicines: dronabinol (P4: THC 0.94 ng/ml, THC-OH ~0.42 ng/ml (<LOQ), THC-COOH 12 ng/ml) and nabiximols (P9). However in the latter patients no exocannabinoids were detected.

| Table 1. Clinical characteristics of patients with TS (for individual data please refer to [12]). |
|---|---|---|---|---|
| Age (male, n = 18, female, n = 2) | N | Mean | SD | Range |
| YGTSS-TTS | 20 | 23.2 | 9.1 | 10–39 |
| Y-BOCS | 20 | 8 | 5.9 | 0–17 |
| PUTS | 20 | 25.8 | 5.7 | 13–36 |
| BDI-II | 20 | 11.8 | 7.9 | 0–29 |
| BAI | 20 | 10.9 | 8.5 | 0–31 |
| WURS-K | 20 | 23.3 | 14.7 | 0–60 |
| CAARS, t-score | 17 | 54.8 | 12.8 | 25–90 |
| DSM-IV symptom list for ADHD | 20 | 3.3 | 2.2 | 0–8 |
| Inattentive | 20 | 2.7 | 2.3 | 0–8 |
| Hyperactivity/Impulsivity | 20 | 61.5 | 10.7 | 41–80 |

TS Tourette syndrome, YGTSS-TTS Yale Global Tic Severity Scale—Total Tic Score, Y-BOCS Yale–Brown Obsessive Compulsive Scale, PUTS Premonitory Urge for Tics Scale, BDI-II Beck Depression Inventory-II, BAI Beck Anxiety Inventory, WURS-K Wender Utah Rating Scale short version, CAARS Conner’s Adult ADHD Rating Scale, ADHD attention-deficit/hyperactivity disorder, BSI Brief Symptom Inventory.
DISCUSSION
This is the first study demonstrating alterations in endocannabinoid levels in adult patients with TS. We found significant elevations of both the endocannabinoids AEA and 2-AG, the endocannabinoid-like ligand PEA, and the metabolite AA in adult patients with TS compared with controls. CSF levels of 2-AG correlated with severity of ADHD. As a trend ADHD symptoms were further correlated to CSF levels of AA. No other correlations could be detected, neither with further clinical data, nor with routine CSF abnormalities.

Alterations of CSF endocannabinoid levels in TS can be interpreted in different ways. First, it can be speculated that elevations of AEA, 2-AG, PEA, and AA are secondary in order to compensate for the presumed striatal dopaminergic hyperinnervation underlying TS. The striatum contains high levels of central cannabinoid CB1 receptors [26]. Although nigrostriatal dopaminergic neurons appear not to contain CB1 receptors, the ECS significantly influences the activity of the dopaminergic system, resulting in clinically relevant alterations of motor activity [10, 27].
In addition to this indirect effect, it has been shown that striatal dopaminergic transmission is also modulated directly via vanilloid TRPV1 receptors [28] a receptor functionally related to the cannabinoid signaling system—and cannabinoid CB2 receptors located on dopaminergic neurons [27]. On the other hand, stimulation of dopamine D2-like receptors increases the levels of AEA in the striatum [29]. Endocannabinoids may counteract the effects of dopamine D2 receptor stimulation, since dopamine D2 receptor-dependent stimulation of the ECS results in an inhibitory feedback mechanism [29]. Thus, in the striatum, there is not only a complex indirect functional interaction between CB1 and dopamine receptors, but endocannabinoids also control directly the dopaminergic neurotransmission [10].

Assuming both that TS is caused by a dopaminergic hyperinnervation and that increased levels of endocannabinoids represent a compensatory mechanism, one would expect that endocannabinoids may reduce increased phasic or tonic dopamine or both. In fact, several lines of evidence support the hypothesis that endocannabinoids may reduce striatal dopaminergic signaling: (i) AEA is a full agonist for TRPV1 receptors [30] and activation of TRPV1 receptors located in nigrostriatal dopaminergic neurons results in direct inhibition of dopamine activity [31]. Therefore, AEA has been referred to a “stop signal for dopamine” [29], (ii) AEA behaves as a hypokinetic substance [31]; (iii) activation of TRPV1 receptors produces hypokinesia in rats [32]; (iv) AEA induced hypokinesia is mediated by a reduction in depolarization-induced neurotransmitter release on dopaminergic terminals [31]; (v) dopamine transmission can be modulated via G protein/adenyl cyclase signal transduction mechanisms shared by both CB1 and dopamine D1/D2 receptors located in basal ganglia neurons [10]; and (vi) only recently, also cannabinoid CB2 receptors have been identified on nigrostriatal dopaminergic neurons [33] suggesting that direct activation of these receptors also modulates striatal dopaminergic transmission [27].

In summary, it can be speculated that in TS dopaminergic hyperinnervation leads to a compensatory increase in endocannabinoids in order to decrease dopaminergic transmission. This assumption is also in line with reported beneficial treatment effects of cannabis-based medicines in TS. In addition, in a pilot study in adult patients with TS (n = 20), it could be demonstrated that further increase of 2-AG by ABX-1431, a highly selective inhibitor of the degradation enzyme monoacylglycerol lipase (MAGL), results in a reduction oftics and premonitory urges [34].

Secondly, it can be speculated that increased endocannabinoids in TS are related to alterations in other neurotransmitter systems than the dopaminergic system, since CB1 receptors are also present on striatal GABAergic interneurons, cholinergic interneurons as well as glutamatergic neurons (for review see [10]). All these neurotransmitters have also been suggested to play a role in the pathophysiology of TS [35].

Thirdly, one might also speculate that alterations in the ECS – and not in other neurotransmitter systems such as the dopaminergic system – represent the primary cause of TS. However, until today there are no other genetic [36], imaging [37], or biochemical studies available reporting about alterations in the ECS in patients with TS.

Fourthly, from our results it cannot be excluded that elevated endocannabinoid levels are simply an epiphenomenon with no pathological relevance.

In humans, a physiological “endocannabinoid tone” has been suggested based on tonically released endocannabinoids [38] and an intact interplay between the endocannabinoids including their production and metabolism and cannabinoid CB1/CB2 and other cannabinoid-like receptors (such as TRPV1 receptors) [39]. Alterations of endocannabinoid levels have been described in several different neurological disorders including Parkinson’s disease [40], epilepsy [41], and multiple sclerosis [42]. Migraine and post-traumatic stress disorder (PTSD) have been suggested to represent so called “endocannabinoid deficiency syndromes”, since in chronic migraine reduced CSF levels of AEA have been detected [43], while patients with PTSD demonstrated an up-regulation of CB1 receptors [44].

Based on clinical findings demonstrating beneficial effects of cannabis-based medicine in patients with TS, one might speculate that TS is also caused by an “endocannabinoid deficiency”. Our results of elevated endocannabinoid levels do not contradict with
this hypothesis, since it can be speculated that the overall endocannabinoid tone is still reduced in TS, for example due to a reduced number or reduced sensitivity of cannabinoid CB1/CB2 receptors or an overactivity of the degradation enzymes MAGL (for 2-AG) and fatty acid amide hydrolysis (FAAH, for AEA). Such an hypothesis in turn would provide a plausible explanation for the fact that several different neurotransmitter systems have been suggested to be involved in the pathophysiology of TS including the dopaminergic, GABAergic, and glutamatergic systems [35].

Furthermore, it is believed that the ECS—in particular a dysregulation of 2-AG signaling—plays an important role in the regulation of chronic stress [45]. Stress, in turn, is the most relevant environmental factor that increases tics [46]. In this context, it is remarkable that stress modulates the ECS by altering the expression level of CB1 receptors, increases 2-AG and reduces AEA (for review see [47]). Since stress-induced reduction of AEA leads to increased dopaminergic signaling, it is not surprising that in TS, levels of endocannabinoids are significantly reduced [48].

When comparing endocannabinoid levels with clinical data, we found correlations between the severity of ADHD and levels of 2-AG. This correlation between endocannabinoid levels and the severity of ADHD is noteworthy, since there is some evidence that the cannabis extract nabiximols is effective in the treatment of ADHD [48] and the activity of FAAH has been found to be decreased in patients with ADHD suggesting dysfunctional AEA degradation in this group of patients [49].

Two patients (P4, P9) received treatment for TS with cannabis-based medicine, however, the latter was tested negative for exocannabinoids. Two further patients (P15, P20) were tested positive for THC or THC-COOH presumably due to recreational use of cannabis. Interestingly, levels of endocannabinoids were at the lower end, but not outside the range found in other patients. In four patients (P 2, 7, 12, 14), we found positive OCBs (further results were reported elsewhere [12]). This result clearly indicates a pathological immune process in terms of an intrathecal production of IgG antibodies. However, we found no differences in endocannabinoid levels with respect to positive OCBs suggesting that elevated endocannabinoid levels in TS are unrelated to these immunological changes.

The following limitations of the study have to be addressed: (i) the sample size is still relatively small. However, this is the first study investigating endocannabinoid CSF levels in TS and lumbar puncture is not routinely performed in patients with TS; (ii) typically tics wax and wane and the assessment of tics (and all other clinical symptoms) were performed only once at the day of lumbar puncture. Since the YGTSS-TTS measures tic severity during the last week, we believe that current tic severity is the most relevant for participating in the study, we do not believe that this has caused any bias in patient selection; (iv) our control group consists of more females and is slightly older compared with the group of patients with TS. While sexual dimorphism in response to cannabinoid ECS in these pathologies; (v) our control group consists of patients with IIH and NPH. Due to ethical reasons we did not recruit a group of healthy controls. However, including patients with IIH and NPH as controls is common practice in CSF studies [50] and there is no evidence suggesting alterations in the ECS in these pathologies; (vi) our control group consists of more females and is slightly older compared with the group of patients with TS. While sexual dimorphism in response to cannabinoid compounds has been reported [51], only scarce data are available on gender differences in brain regions, while no evidence on gender differences in circulating endocannabinoid levels have been reported due to our knowledge [52]. Moreover, there is no

| Table 3. Correlation of CSF endocannabinoids with clinical data in patients with TS. |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                | Age            | Age at tic onset | Tic severity (YGTSS-TTS) | OCD (YBOCS) | Premonitory urges (PUTS) | ADHD (CAARS) | ADHD (WURS-K) | Depression (BDI-II) |
| AEA            | Pearson correlation | 0.179 0.020 | −0.122 0.014 | 0.131 0.337 | −0.365 0.199 |
| Sig. (2-tailed) | 0.449 0.935 | 0.607 0.953 | 0.583 0.185 | 0.113 0.400 |
| N              | 20 20 | 20 20 | 20 20 | 17 20 |
| 2-AG           | Pearson correlation | −0.121 0.108 | −0.036 0.111 | 0.097 0.171 | 0.750 0.241 |
| Sig. (2-tailed) | 0.611 0.649 | 0.881 0.641 | 0.685 0.512 | 0.000 0.307 |
| N              | 20 20 | 20 20 | 20 20 | 17 20 |
| AA             | Pearson correlation | 0.147 0.022 | −0.019 0.137 | 0.001 −0.637 | 0.593 0.023 |
| Sig. (2-tailed) | 0.536 0.925 | 0.936 0.566 | 0.966 0.006 | 0.006 0.924 |
| N              | 20 20 | 20 20 | 20 20 | 17 20 |
| PEA            | Pearson correlation | −0.003 0.053 | −0.233 0.193 | 0.467a −0.113 | 0.186 0.337 |
| Sig. (2-tailed) | 0.989 0.824 | 0.322 0.414 | 0.038 0.667 | 0.433 0.146 |
| N              | 20 20 | 20 20 | 20 20 | 17 20 |

TS Tourette syndrome, CSF cerebrospinal fluid, AEA “N”-arachidonylethanolamine, 2-AG 2-arachidonoylglycerol, PEA palmitoyl ethanolamide, AA arachidonic acid, YGTSS-TTS Yale Global Tic Severity Scale—Total Tic Score, OCD obsessive-compulsive disorder, YBOCS Yale–Brown Obsessive Compulsive Scale, PUTS Premonitory Urge for Tics Scale, ADHD attention-deficit/hyperactivity disorder, CAARS Conner’s Adult ADHD Rating Scale, WURS-K Wender Utah Rating Scale short version, BDI-II Beck Depression Inventory-II. 

*Significant after Bonferroni correction for multiple comparisons.
reported evidence that levels of endocannabinoids in CSF are influenced by sex or this minor age difference [52]; and (vi) data obtained from one control subject (CS) were excluded from further analyses, since results of endocannabinoids were far outside the normal ranges at our lab. Even a critical review (including clinical data, procedure of lumbar puncture, further processing with CSF in the labs at Hannover Medical School and the Institute of Physiological Chemistry Mainz) did not lead to a conclusive explanation for this finding. However, even when not excluding this outlier from further analyses, CSF levels of AEA were still significantly elevated.

In conclusion, we were able to demonstrate for the first time elevated CSF levels of AEA, 2-AG, PEA, and AA in patients with TS suggesting that the ESC is involved in the pathophysiology of the disease. However, it cannot entirely be excluded that elevated endocannabinoid levels are simply an epiphenomenon. Because of the complex bidirectional interaction between the ECS and several other neurotransmitter systems, one might speculate that increased levels of endocannabinoids represent a secondary mechanism in order to compensate for dopaminergic hyperinnervation or, alternatively, represent a primary cause of TS and changes in other neurotransmitter systems are secondary due to the complex interaction between these systems.

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**AUTHOR CONTRIBUTIONS**

(1) Research project: KR MV: A. Conception, B. Organization, C. Execution; LB: A. Conception, B. Organization, C. Execution; BL: A. Conception; TS: B. Organization; CB: B. Organization, C. Execution; KWS: A. Conception, B. Organization, C. Execution; FM: C. Execution . (2) Statistical Analysis: KR MV: A. Design, C. Review and Critique; LB: A. Design, B. Execution, C. Review and Critique; BL: C. Review and Critique; TS: C. Review and Critique; CB: A. Design, KWS: LB: A. Design, B. Execution, C. Review and Critique; FM: C. Review and Critique. (3) Manuscript: KR MV: A. Writing of the first draft, B. Review and Critique, LB. B. Review and Critique, BL: B. Review and Critique, TS: B. Review and Critique, CB: B. Review and Critique, KWS: B. Review and Critique, FM: C. Review and Critique. All authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**ADDITIONAL INFORMATION**

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