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Letter to the Editor

Cerebrospinal fluid levels of sphingolipids associate with disease severity in first episode psychosis patients

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Alterations in brain lipid composition have been described in schizophrenia (Hamazaki et al., 2015; Schmitt et al., 2004; Amminger et al., 2012), a disease characterized by positive and negative symptoms as well as with deficits in cognitive function (Fatouros-Bergman et al., 2014). Specifically, decreased levels of sphingomyelins and hexosylceramides in thalamus (Schmitt et al., 2004) and reduced gene expression of the sphingolipid pathway in prefrontal cortical samples (Narayan et al., 2009) have been described, as well as an association between sphingomyelin levels in red blood cell (RBC) membranes and symptom severity (Tessier et al., 2016). Sphingomyelins and hexosylceramides (Supplemental Material) are sphingolipids that possess structural as well as signaling functions in the brain. In a previous study (Checa et al., 2015), we found increased levels of $HexCer_{24:1}$ in the cerebrospinal fluid (CSF) of patients with schizophrenia, who served as part of the disease control group. This led us to hypothesize that the observed alterations may form part of pathophysiological mechanisms of the disease. Using liquid chromatography tandem mass spectrometry (Supplementary Material) we measured CSF levels of $HexCer_{24:1}$ in cohorts with first episode psychosis (FEP) patients, chronic schizophrenia, or schizoaffective disorder. Levels of other hexosylceramides and sphingomyelins were measured as an exploratory aim.

FEP patients ($n = 44$) were recruited within the Karolinska Schizophrenia Project (Orhan et al., 2017), whereas chronic patients ($n = 23$) were included from Linköping (Skogh et al., 2011). Twenty-five of 44 FEP patients were drug naïve to antipsychotic medication. Psychotic symptoms and global functioning were assessed and measured with Positive and Negative Syndrome Scale (PANSS), Global Assessment of Functioning (GAF) and Clinical Global Impression (CGI). In the FEP cohort, patients on antipsychotic medication presented lower GAF symptoms scores relative to drug-naïve patients ($p = 0.026$) and higher CGI scores ($p = 0.077$), indicating a more severe stage of the disease (Supplementary Material). All chronic patients were on treatment with oral olanzapine. Sphingolipids from two control groups of healthy volunteers, age-matched with FEP patients and patients with chronic schizophrenia were analyzed ($n = 20$ and $n = 10$, respectively).

CSF levels of sphingolipids did not differ between FEP patients and healthy controls or between chronic patients and healthy controls (Table 1). Amongst FEP patients, the levels of $HexCer_{24:1}$ ($p = 0.011$) were higher in patients that had received antipsychotic treatment relative to those who were drug-naïve. Higher CSF levels of $HexCer_{24:1}$ were associated with more severe symptoms in FEP patients, as shown by their positive correlations with positive ($r_s = 0.32$, $p = 0.035$), negative ($r_s = 0.31$, $p = 0.038$), general ($r_s = 0.30$, $p = 0.045$) and total PANSS ($r_s = 0.36$, $p = 0.016$) as well as with CGI ($r_s = 0.34$, $p = 0.008$) scores. Moreover, there was a negative correlation with GAF scores ($r_s = -0.35$, $p = 0.021$). In chronic schizophrenia patients, no associations were observed between levels of sphingolipids and positive, negative, general or total BPRS scores (Table 1) and the levels of sphingolipids did not associate with GAF symptoms. Levels of $HexCer_{24:1}$ were negatively associated with duration of illness ($r_s = -0.51$; $p = 0.014$) in long-term medicated patients (Supplementary Material). Though $HexCer_{24:1}$ presented the most consistent associations, exploratory analyses in other sphingolipids showed the same trends (Table 1).

Previously, a negative association was reported between PANSS and sphingomyelin levels in RBC in clinically stable outpatients with schizophrenia (Tessier et al., 2016). Also, in our previous study we showed higher CSF sphingolipid levels in multiple sclerosis patients, where lower brain levels of these compounds had previously been reported (Checa et al., 2015). Our observations of positive associations in FEP patients between CSF sphingolipids and severity of illness and psychotic symptoms would be in accordance with these results. Moreover, they are in line with the previously reported lower mRNA levels of enzymes in the sphingolipid biosynthetic pathway found in prefrontal cortical samples of patients with schizophrenia with short term illness, which were not observed in patients in later stages of the disease (Narayan et al., 2009). For later stage patients, compensatory changes in the phospholipid metabolism have previously been shown (Keshavan et al., 1993). One interpretation of the available data is that demyelination could occur specifically in the early stages of schizophrenia, and that this could be part of the disease mechanism in the development of psychosis. This opens the door to measuring selected sphingolipids as disease markers or for monitoring treatment effects.

The search for markers of progression in schizophrenia has gained increased attention during the last few years. Using two cohorts of well-characterized patients and quantifying a selected sphingolipid panel including three different fatty acid chains, we show that CSF levels of $HexCer_{24:1}$ may reflect different myelination status at different stages of the disease. Results from prior studies as well as this study suggest that future work evaluating the associations between lipids and schizophrenia should both focus on the severity of the symptoms as well as on the stage of the disease. It would also be of significant clinical utility to screen for the observed shifts in sphingolipids in RBC membranes given the relative ease of obtaining blood samples compared to CSF.

Potential conflicts of interest

There are no commercial associations that might pose a conflict of interest in connection with the manuscript. SE has received grant support from AstraZeneca and Jansen Pharmaceuticals as principal investigator, has served as a one-off speaker for Roche pharmaceuticals and participated in workshops organized by Otsuka Pharmaceuticals. SC has received grant support from AstraZeneca as a co-investigator, and has served as a one-off speaker for Otsuka-Lundbeck. FP has received unrestricted academic research grants

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Table 1
Sample characteristics and associations of sphingolipids with clinical scores.

MEDIAN [Interquartile range] (n)*			
Characteristic	Healthy controls ($n = 20$)	First Episode Psychosis Patients ($n = 44$)	p-Value
Age, years	25.0 [21.8–27.3] (20)	30.0 [25.8–36.0] (44)	<0.001[a]
Gender, male/female	11/9	27/17	0.837[b]
BMI, kg m^{-2}	22.4 [21.1–24.5] (15)	22.8 [20.6–25.1] (42)	0.537[a]
Smokers, %,	0% (20)	9.1% (44)	–
DUP, months	–	6.0 [2.0–18] (39)	–
Under antipsychotic treatment, %	0%	43.2% (44)	–
Days of antipsychotic treatment, days	–	14 [9–19] (19)	–
$HexCer_{24:1}$ (Primary aim)	29.0 [25.5–33.9] (20)	31.2 [26.0–41.8] (44)	0.221[c]
$HexCer_{16:0}$ (Exploratory aim)	0.42 [0.38–0.45] (20)	0.39 [0.34–0.44] (44)	0.324[c]
$HexCer_{18:0}$ (Exploratory aim)	7.2 [5.7–9.8] (20)	7.2 [6.5–9.0] (44)	0.712[c]
$SM_{16:0}$ (Exploratory aim)	151 [140–193] (20)	7.2 [6.5–9.0] (44)	0.672[c]
$SM_{18:0}$ (Exploratory aim)	235 [192–263] (20)	214 [188–263] (44)	0.757[c]
$SM_{24:1}$ (Exploratory aim)	104 [89–115] (20)	96 [84–140] (44)	0.701[c]

MEDIAN [Interquartile range] (n)*			
Characteristic	Healthy controls ($n = 10$)	Chronic schizophrenia/schizoaffective patients ($n = 23$)	p-Value
Age, years	23.0 [21.0–27.0] (10)	35.5 [30.5–41.0] (23)	0.007[a]
Gender, male/female	10/0	15/8	
BMI, kg m^{-2}	23.1 [21.6–26.1] (10)	26.1 [22.4–26.9] (23)	0.295[a]
Smokers, %	0 (7)	43.5 (23)	–
Under antipsychotic treatment, %	–	100% (23)	–
Dose of Olanzapine, mg	–	10.0 [7.5–17.5] (23)	
Years of illness	–	11.5 [6.0–19.5] (23)	–
$HexCer_{24:1}$ (Primary aim)	32.1 [28.0–34.9] (10)	29.0 [24.0–31.8] (23)	0.343[c]
$HexCer_{16:0}$ (Exploratory aim)	0.30 [0.25–0.52] (10)	0.25 [0.22–0.32] (23)	0.050[c]
$HexCer_{18:0}$ (Exploratory aim)	3.70 [2.80–3.82] (10)	3.39 [2.75–3.58] (23)	0.347[c]
$SM_{16:0}$ (Exploratory aim)	168.7 [152.2–186.7] (10)	158.0 [138.1–170.7] (23)	0.363[c]
$SM_{18:0}$ (Exploratory aim)	211.5 [178.4–235.4] (10)	174.9 [152.1–210.1] (23)	0.137[c]
$SM_{24:1}$ (Exploratory aim)	96.9 [89.8–119.9] (10)	94.4 [86.3–112.6] (23)	0.686[c]

Associations of sphingolipids with clinical scores (r_s)						
First Episode Psychosis patients ($n = 44$)	Primary aim	Exploratory aim				
	$HexCer_{24:1}$ (r_s)	$HexCer_{16:0}$ (r_s)	$HexCer_{18:0}$ (r_s)	$SM_{16:0}$ (r_s)	$SM_{18:0}$ (r_s)	$SM_{24:1}$ (r_s)
PANSS						
Positive	0.32*	0.19	0.03	0.31*	0.17	0.24
Negative	0.31*	0.21	0.06	0.28†	0.21	0.30*
General	0.30*	0.25	0.27†	0.25	0.17	0.18
Total	0.36*	0.28†	0.18	0.33*	0.23	0.29†
Level of functioning						
GAF Symptom	−0.35*	−0.29†	−0.25	−0.23	−0.12	−0.30*
GAF Function	−0.15	−0.03	−0.19	−0.26†	−0.17	−0.22
CGI Scores	0.39**	0.13	0.30†	0.21	0.08	0.25
Schizophrenia and schizoaffective disorders patients (n = 23)						
BPRS						
Positive	−0.10	−0.08	0.04	0.05	−0.05	0.06
Negative	0.17	−0.09	0.19	−0.05	0.11	0.09
General	−0.02	0.09	0.20	0.14	0.12	0.12
Total	0.02	0.02	0.20	0.08	0.06	0.13
Level of functioning						
GAF Symptom	0.07	0.06	−0.17	−0.21	−0.15	−0.12

r_s: Spearman's rank correlation; Concentrations in nM.
Abbreviations: FEP = First-episode psychosis, BMI = Body Mass Index, DUP = Duration of Untreated Psychosis, PANSS = Positive and Negative Syndrome Scale, GAF = Global Assessment of Functioning, CGI = Clinical Global Impression BPRS = Brief Psychiatric Rating Scale.
[a] 2 tailed t-test.
[b] χ^2–test.
[c] Mann-Whitney U test.
† $p < 0.1$.
* $p < 0.05$.
** $p < 0.01$.

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Contributors

AC, CEW, FP and SE designed the study; AM, LF, LS, MS, SC, ES, MLD and FP participated in patients and controls recruitment and assessment; AC acquired the sphingolipid data; AC, AM and LS performed data analysis; AC, AM, SE and CEW drafted the manuscript. All authors contributed to the interpretation of the results, provided critical revision of the manuscript and approved its final version.

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Appendix A. Supplementary Material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.03.029.

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