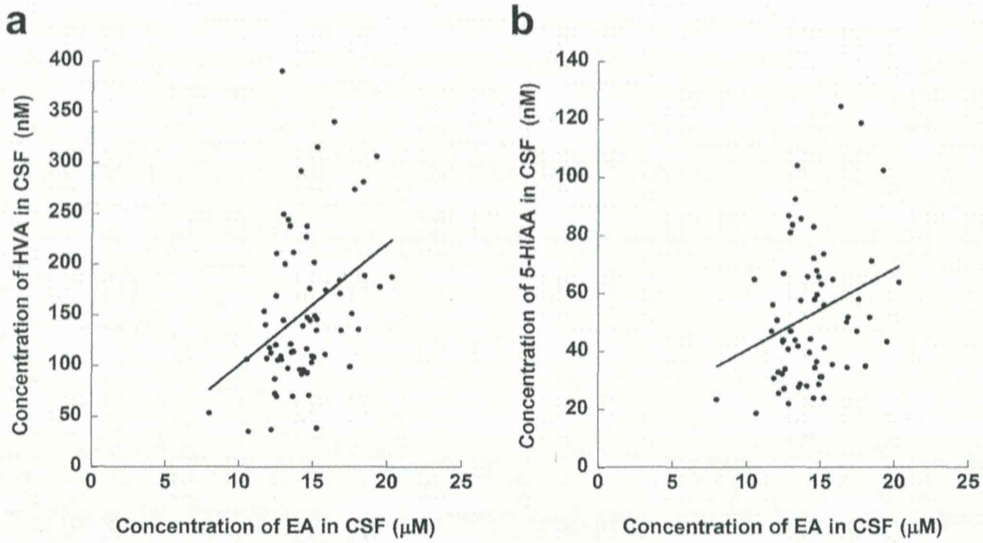

Figure 3 | Scatter plots and regression lines for the relationships of EA with HVA and 5-HIAA in CSF. Partial correlation test controlling for age and sex was performed in healthy controls ($N = 54$) and unmedicated patients with major depressive disorder ($N = 13$). Significant correlations of EA with (a) HVA and (b) 5-HIAA in CSF are shown. Abbreviations: EA, ethanolamine; CSF, cerebrospinal fluid; HVA, homovanillic acid; 5-HIAA, 5-hydroxyindoleacetic acid.

than in controls. However, there was no significant difference between our unmedicated patients ($N = 11$) and controls (629.5 ± 72.9 vs. 644.3 ± 108.8 μM, $F = 0.046$, $df = 1$, $P = 0.83$, 95% CI: −69.33 to 55.89). Therefore, the observed increase in glutamine in our total subjects may be attributable to medication. Regarding CSF GABA, several previous reports[18,19,21,28] showed its decrease in depressed subjects; however, we observed no significant differences between patients and controls, which is in line with other studies[17,20,22]. Recently, Kaddurah-Daouk *et al.*, who employed a metabolomics-based approach, reported that methionine was increased in remitted MDD patients compared with depressed patients and healthy controls[26]. Our subjects showed similar results. Although CSF methionine levels did not differ significantly between the currently depressed patients and controls, our remitted patients had significantly higher CSF methionine levels than depressed patients (4.1 ± 1.2 vs. 3.3 ± 0.9 μM, $F = 9.1$, $df = 1$, $P = 0.0041$; 95% CI: 0.31 to 1.57, ANCOVA) and controls (vs. 3.5 ± 0.8, $F = 5.7$, $df = 1$, $P = 0.020$; 95% CI: 0.11 to 1.29). Methionine might be involved in the recovery processes of MDD and could be a biomarker for remission.

The significantly higher levels of CSF EA in remitted patients compared with depressed patients suggest that CSF EA levels might be state-dependent. In line, our Low-EA patients showed a higher HAMD-17 total score than the High-EA group. Vagus nerve stimulation (VNS), which is effective for MDD patients and alters the metabolites of neurotransmitters[37], was reported to elevate CSF EA levels in epileptic patients[38]. VNS may exert its effect through mechanisms that increase central EA. Longitudinal studies are warranted to examine whether antidepressant treatments increase CSF EA.

When we defined abnormally low EA levels based on the 5th percentile of the controls, approximately 40% of the depressed patients fell into this range, suggesting that a substantial proportion of subjects with MDD could be distinguished from normal subjects based on CSF EA levels, which would be useful for diagnosis. MDD patients with low CSF EA levels may constitute a subtype of MDD. Indeed, the Low-EA group was characterized by higher 'Core' and 'Somatic Anxiety' symptoms. In addition, we found a significant positive correlation between CSF EA and HVA and 5-HIAA levels, suggesting that MDD characterized by low CSF EA levels reflects impaired dopaminergic and serotonergic functions in the CNS, possibly due to synaptic dysregulation by an altered endocannabinoid system (see below).

Since most of our patients were medicated, the observed decrease in CSF EA may be attributable to medication. However, this possibility is unlikely because CSF EA was decreased in unmedicated patients compared with controls; there was no significant difference in CSF EA levels between medicated and unmedicated patients; and there was no significant correlation between CSF EA levels and the dose of any class of psychotropic drugs. Our results therefore suggest that CSF EA could be a useful biomarker even in medicated patients. With respect to the effect of antidepressants, we found a significant correlation with CSF isoleucine levels even after correcting for multiple comparisons. To our knowledge, no study has examined the effect of antidepressants on CSF amino acid levels; therefore, further studies are warranted.

EA is closely related to endocannabinoid signaling in the CNS (see Supplementary Fig. S4). EA is both a precursor to, and a metabolite of, anandamide (*N*-arachidonoylethanolamine), a ligand for cannabinoid receptors (CBs), and transient receptor potential vanilloid type 1 (TRPV1). The endocannabinoid system is implicated in depression, suicide, and stress-related affective disorders[39]. CB_1 receptor density is high at presynaptic axon terminals, where it functions to inhibit neurotransmitter release[40]. This may substantiate our

Table 4 | Partial correlations between levels of CSF substances and EA concentrations

	Statistics			
Substances	*r*	*df*	*P*	95% CI
Total protein	−0.055	63	0.66	−0.30 to 0.19
Glucose	−0.075	63	0.55	−0.31 to 0.17
Chloride	0.077	63	0.54	−0.17 to 0.31
HVA	0.36	63	**0.0030** [1]	**0.13 to 0.56**
MHPG	0.14	63	0.27	−0.11 to 0.37
5-HIAA	0.29	63	**0.019**	**0.051 to 0.50**

[1]Significant *P*-values in bold type.
Abbreviations: CSF, cerebrospinal fluid; EA, ethanolamine; CI, confidence interval; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylethyleneglycol; 5-HIAA, 5-hydroxyindoleacetic acid.

observation that CSF EA was correlated with HVA and 5-HIAA levels. In human studies, inconsistent results have been reported on serum endocannabinoid levels in MDD[41–43]. One study found no significant difference in the CSF anandamide level between MDD patients and controls, although it was elevated in unmedicated patients with schizophrenia[44]. Anandamide is synthesized on demand, binds with high affinity to extracellular CB_1 receptors, and is rapidly inactivated by active transport into neurons, followed by hydrolysis[45]. EA might be a stable surrogate marker for the anandamide system.

Decreased CSF EA may be due to inflammatory responses that have been implicated in MDD[46]. We previously reported elevated CSF IL-6 levels in MDD[47] suggesting the involvement of neuroinflammation. In the inflammatory process, activation of microglia and upregulation of cyclooxygenase-2 may facilitate conversion of EA to *N*-acylethanolamines or prostaglandin H_2 ethanolamide[48,49].

There are several limitations to this study. Firstly, the numbers of unmedicated patients with MDD ($N = 13$) and remitted individuals ($N = 10$) were small. However, we detected a significant difference in CSF EA levels between unmedicated patients and controls; and between depressed and remitted patients, which suggests large effect sizes. Secondly, the measurement of the CSF sample took place in a real-world setting; the majority of patients were medicated, and sampling was not performed after fasting or at a fixed time. However, we did not observe any correlation of EA with psychotropic medication or CSF sampling time. This makes CSF EA a feasible biomarker for everyday use in the clinical setting. Nevertheless, studies are necessary to elucidate the possible effects of fasting. Thirdly, there were missing values for several amino acids (see Table 2), which were likely due to small values below the detection limit and might have caused false negative results. Fourthly, small proportion of patients ($N = 13$) received antipsychotic medication, which may have an effect on CSF EA levels. However, there was no significant correlation between daily chlorpromazine equivalent doses of antipsychotics and CSF EA levels; therefore, the possible effect might be minimal. Finally, we obtained data only for MDD patients and controls. Further studies on other neuropsychiatric disorders are necessary to determine whether low EA is specific to MDD.

In conclusion, we found, for the first time, that CSF EA levels were reduced independently of medication in a substantial proportion (40%) of depressed MDD patients. Such patients had characteristic symptomatology (i.e., 'Somatic Anxiety') and CSF monoamine metabolite profiles (i.e., reduced HVA and 5-HIAA), and thus constitute a subtype of MDD.

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Author contributions

S.O. designed the study, managed the literature searches, profiled the CSF samples by HPLC, undertook the statistical analyses, and wrote the draft of the manuscript. K.H. and Y.Y. recruited the participants. K.H. and D.S. diagnosed the participants, and collected the CSF samples. K.H. selected the sample set. Y.Y. and R.M. made psychological assessments. R.M. created and maintained database system. M.O., H.H. and T.T. screened the participants and diagnosed the patients. Y.O. and H.S. performed the CE-TOF-MS measuring for data validation. N.M. and J.M. reviewed the draft and gave critical comments on the manuscript. T.H., S.Y. and T.N. contributed to the recruitment of clinical volunteers. H.K. supervised the entire project and gave critical comments on the manuscript. All authors contributed to and have approved the final manuscript.

Additional information

Supplementary information accompanies this paper at http://www.nature.com/scientificreports

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新版

基礎から学ぶ 学校保健

瀧澤利行　編著

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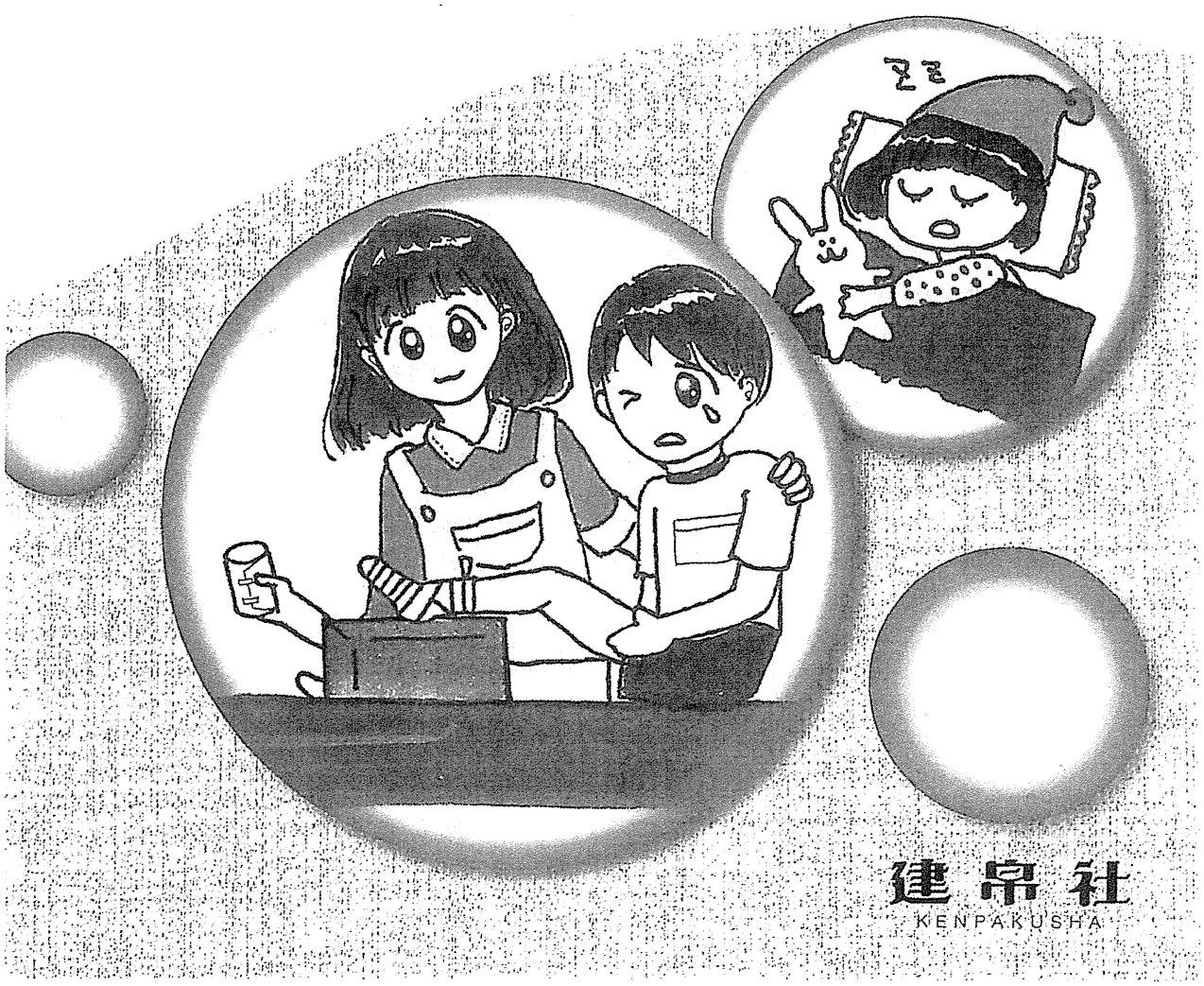

建帛社
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6）起立性調節障害〔orthostatic disregulation：OD〕

起立性調節障害は，自律神経が失調し，起立時の循環器系の調節が不十分となることにより起こる。主な症状は立ちくらみ，脳貧血（脳の血液循環が悪くなり起こる）などである。診断は，従来表3-2の基準によって行われているが，2006（平成18）年に日本心身医学会からも診断・治療ガイドラインが出されている。

表3－2　OD診断基準

大症状	A）立ちくらみあるいはめまいを起こしやすい B）立っていると気持ちが悪くなる。ひどくなると倒れる C）入浴時あるいはいやなことを見聞きすると気持ちが悪くなる D）少し動くと動悸あるいは息切れがする E）朝なかなか起きられず，午前中調子が悪い
小症状	a）顔色が青白い b）食欲不振 c）強い腹痛をときどき訴える d）倦怠あるいは疲れやすい e）頭痛をしばしば訴える f）乗り物に酔いやすい g）起立試験で脈圧狭小16 mmHg以上 h）起立試験で収縮期血圧低下21 mmHg以上 i）起立試験で脈拍数増加21回/分以上 j）起立試験で立位心電図のTⅡの0.2 mV以上の減高，その他の変化
判断	大1・小3，大2・小1，大3，以上で器質性疾患を除外できた場合をODとする

7）貧　　血〔anemia〕

貧血は血色素（ヘモグロビン）濃度の低下した状態であり，血色素による酸素運搬が減少することにより，顔色が悪い，動悸，倦怠感などがみられる。学齢期には，血色素の成分である鉄分の不足による鉄欠乏性貧血が多い。身体発育に伴い鉄需要が増しているので，鉄を含めてバランスよい食事摂取をすることが重要である。

2．学校でみられるこころの健康問題

いじめ，不登校，家庭内暴力や自殺などこころの健康の重要性が高まっている。そこで，これらの理解を深めるために，学校現場でみられるこころの問題を簡単に概説する。

1）ひきこもり

いろいろな定義があるが，ここでは精神科医である斎藤環の定義を紹介する。それによると，**ひきこもり**とは「20代後半までに問題化し，6ヶ月以上，自宅に引きこもって社会参加しない状態が持続しており，他の精神疾患がその第一の原因とは考えにくいもの」としている[1]。10代後半から20代前半に起こり，男性に多い。失恋やケガなど周囲からみると些細な挫折体験をきっかけにひきこもることが多い。自宅の自室にひきこもり，家

族ともコミュニケーションを絶つ例も少なくない。精神的には不安や焦燥が強く，他者の評価に敏感で，家人に猜疑的となり家庭内暴力に発展する場合がある。このような状況から，精神疾患を併発する場合もあるので注意が必要である。

特筆すべきは，ひきこもりの60％以上が不登校経験者であり，いったんひきこもると10年以上も長期化することが少なくないので，不登校の段階での適切な対処が重要と考えられている。

2）心理的発達の障害〔ICD-10：F 8〕（第9章参照）

① 自閉症〔autism〕　カナー（L. Kanner）が「聡明な容貌・常同行動・高い記憶力・機械操作の愛好」などを特徴とする一群の幼児に対し，**自閉症（オーティズム）**と名づけた[2]。その後，親の育て方で自閉症になるなどの間違った認識があったが，現在は先天性の脳障害であることがわかり，全般性発達障害の小児自閉症（自閉症）に分類されている。この障害には自閉症状と知的障害の2つの障害がいろいろな割合で存在し，多くは3歳までに気づかれる。知的障害がないものはアスペルガー症候群（自閉症スペクトラム障害，ASD）として自閉症とは区別されている。

自閉症状で問題となるのはコミュニケーションの障害や興味や関心が限局していることで，具体的には「視線を合わせない」，「おうむ返しの返答」，「友達と遊ばない」，「変化を嫌い，儀式などに固執する」，「思いどおりにならないとひどい癇癪を起こしたり，手首を噛むなどの自傷行為を行う」ことである。今のところ治療法はなく，療育が中心となり，補助的に薬物治療を行うこともある。

② 学習障害〔learning disorders〕　学習障害は，精神科疾患として心身発達の障害に分類されている。しかし，診断を受けても医学的治療法がないことなどから，医療場面より教育現場で問題となる。

文部科学省は，「学習障害とは，基本的には全般的な知的発達に遅れはないが，聞く，話す，読む，書く，計算する又は推論する能力のうち特定のものの習得と使用に著しい困難を示す様々な状態を指すものである。学習障害は，その原因として，中枢神経系に何らかの機能障害があると推定されるが，視覚障害，聴覚障害，知的障害，情緒障害などの障害や，環境的な要因が直接の原因となるものではない」（文部科学省，1999年）と定義している。

実際の学校現場では，学習の障害よりもむしろ随伴する自己制御困難（授業中に私語が多い，ルールを守れない）や対人関係困難（人の嫌がることを言う，自分勝手な言動）が問題になることが多い。学力の向上だけにとらわれず，社会生活に適応できる援助が重要と思われる。

3）注意欠陥多動性障害〔attention-deficit hyperactivity disorder；ADHD，ICD-10：F 90〕（第9章参照）

ADHDはICD-10では多動性障害に分類され，いわば極端に落ち着きがなく注意散漫で衝動的な行動をとる傾向のある子どもである。生後5か月ごろに発症し，女子より男子に

多い。衝動的で，事故を起こしやすく，不注意から軽率な規則違反を起こし，親の躾(しつけ)の問題と誤解されることがある。しかし，これは脳の機能障害が原因と考えられ，親の躾が原因ではない。知的障害を伴わなければ，知能は普通である。不注意や衝動性などから学業の成績によい時と悪い時，波があることが多い。

薬物療法としては行動を鎮静するために覚醒剤の一種であるメチルフェニデートなどが効果を示す場合がある。いずれにせよ薬物療法は補助的であり，学校と家庭が連携して療育を行うことが肝要と思われる。むやみにしかったり，教師と親の対応がまったく異なるなど学校と家庭の療育の連携が悪いと，反抗挑戦性障害や行為障害，最悪の場合犯罪に発展する場合もあると考えられている（DBD マーチ，DBD：disruptive behavior disorder，破壊的行動障害）[1]。児童・思春期の精神疾患はいずれも学校や家庭の連携ある対応が重要であるが，ADHD においてはその重要性はさらに高いと思われる。

4）精神疾患（第 10 章参照）

厚生労働省の 2008（平成 20）年の調査では，精神疾患の患者は 323 万人にのぼり，237 万人の糖尿病，152 万人のがんなど他の 4 大疾病を大幅に上まわった。このような現状を受け，同省は 2013（平成 25）年 4 月から精神疾患をがん，脳卒中，急性心筋梗塞，糖尿病と並ぶ 5 大疾病と位置づけ，5 疾病 5 事業をスタートさせた。この事業は精神疾患の早期発見と共に地域での精神医療（病院・診療所・訪問看護ステーションの連携強化など）の向上を目指している。

§2．学校でみられる生活習慣病

成人の生活習慣病と同様に学齢期においても，近代的生活による運動不足，過食などに起因する肥満や高血圧，糖尿病，脂質異常症は動脈硬化を促進し，心疾患および脳血管疾患のリスクとなっている。

1．糖　尿　病〔diabetes〕

糖尿病には，免疫異常等による膵臓のインスリン分泌不全である 1 型と，過食・運動不足等によりインスリンの作用・分泌が低下する 2 型がある。1 型は，インスリン注射が必要である。

2 型は，食事療法により食事を適量バランスよく食べて肥満を改善すること，運動により細胞のインスリン感受性を向上させることなどでコントロールする。

2．高　血　圧〔hypertension〕

高血圧は，体質に加え，肥満や食塩過剰摂取により起こるので，それらの改善が肝要である。