Increase of urinary 5-hydroxyindoleacetic acid excretion but not serum chromogranin A following over-the-counter 5-hydroxytryptophan intake

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BACKGROUND: 5-hydroxyindoleacetic acid (5-HIAA) excretion is commonly measured for biochemical detection of carcinoid tumours. A 77-year-old woman was referred for elevated 24 h urine 5-HIAA excretion (510 µmol/day; normal is less than 45 µmol/day) and serum chromogranin A (CgA) (72.1 U/L; normal is less than 18 U/L), both subsequently normalized after discontinuation of 5-hydroxytryptophan (5-HTP). 5-HTP, a precursor of serotonin, is not commonly listed as a substance that increases 5-HIAA levels in urine. The effect of 5-HTP on CgA has not been previously described.

OBJECTIVES: To determine whether, and to what extent, oral 5-HTP increases urine 5-HIAA excretion and serum CgA levels in healthy volunteers.

PATIENTS AND METHODS: A randomized, prospective, double-blind, placebo-controlled crossover study, with a four-day washout period, was performed in a general community setting. Eight healthy subjects aged 22 to 58 years were recruited by advertising. Bedtime ingestion of 5-HTP 100 mg/day was compared with placebo ingestion for 10 days. Twenty-four hour urine excretion of 5-HIAA and serum CgA were the main outcome measures.

RESULTS: Median (range) urinary 5-HIAA excretion was 204 µmol/day (22 µmol/day to 459 µmol/day) during 5-HTP intake, compared with 18 µmol/day (12 µmol/day to 36 µmol/day) during placebo intake (P=0.017). 5-HTP did not affect clinical symptoms or serum CgA levels.

CONCLUSIONS: Oral 5-HTP increases urinary 5-HIAA excretion with considerable interindividual variation. In a small number of subjects, oral 5-HTP did not affect serum CgA levels. Therefore, increased 5-HIAA levels with normal CgA levels may suggest 5-HTP ingestion. The use of over-the-counter 5-HTP should be excluded as the cause of increased urinary 5-HIAA levels before initiating diagnostic tests to search for a carcinoid tumour. 5-HTP should be added to popular references as a substance that may cause increased 5-HIAA excretion.

Key Words: *5-hydroxytryptophan; 5-hydroxyindoleacetic acid; Carcinoid; Chromogranin A*

Une augmentation de l'excrétion urinaire d'acide 5-hydroxy-indole-acétique, mais pas de chromogranine A sérique, après la prise de 5-hydroxytryptophane en vente libre

HISTORIQUE : On mesure souvent l'excrétion d'acide 5-hydroxy-indole-acétique (5-HIAA) pour la détection biochimique des tumeurs carcinoïdes. Une femme de 77 ans a subi une telle évaluation en raison d'une excrétion urinaire élevée de 5-HIAA sur 24 heures (510 µmol/jour; la normale est inférieure à 45 µmol/jour) et d'une chromogranine A (CgA) sérique (75 U/L; la normale est inférieure à 18 U/L), toutes deux revenues à la normale après l'abandon du 5-hydroxytryptophane (5-HTP). Le 5-HTP, un précurseur de la sérotonine, n'est pas souvent désigné parmi les substances qui accroissent les taux de 5-HIAA dans l'urine. L'effet du 5-HTP sur le CgA n'a pas été décrit auparavant.

OBJECTIFS : Déterminer si le 5-HTP par voie orale accroît l'excrétion urinaire et les taux de CgA sérique, et dans quelle mesure, chez des volontaires en santé.

PATIENTS ET MÉTHODOLOGIE : Les auteurs ont procédé à une étude transversale prospective aléatoire à double insu et contrôlée contre placebo comportant une période d'élimination de quatre jours auprès du grand public. Ils ont recruté huit sujets en santé de 22 à 58 ans au moyen de publicités. Ils ont comparé l'ingestion de 100 mg/jour de 5-HTP au coucher à l'ingestion d'un placebo pendant dix jours. Les principales mesures d'issue étaient l'excrétion urinaire de 5-HIAA au bout de 24 heures.

RÉSULTATS : L'excrétion urinaire médiane (fourchette) de 5-HTP était de 204 µmol/jour (22 µmol/jour à 459 µmol/jour) pendant la prise de 5-HTP, par rapport à 18 µmol/jour (12 µmol/jour à 36 µmol/jour) pendant la prise d'un placebo (P=0,017). Le 5-HTP n'influait pas sur les symptômes cliniques ou les taux de CgA sérique.

CONCLUSIONS : Le 5-HTP par voie orale accroît l'excrétion urinaire de 5-HIAA et comporte d'importantes variations entre individus. Chez un petit nombre de sujets, il n'influe pas sur les taux de CgA sérique. Par conséquent, un taux plus élevé de 5-HIAA associé à un taux de CgA normal peut laisser supposer l'ingestion de 5-HTP. Il faut exclure la possibi lité d'utilisation de 5-HTP en vente libre parmi les causes d'augmentation des taux urinaires de 5-HIAA avant de procéder à des tests diagnostiques pour dépister des tumeurs carcinoïdes. Dans les sources populaires, il faut ajouter le 5-HTP aux substances susceptibles de provoquer une augmentation de l'excrétion de 5-HIAA.

5-hydroxyindoleacetic acid (5-HIAA) is a product of serotonin metabolism that is excreted in the urine. It is used as a first-line test for biochemical detection of suspected carcinoid syndrome, in which 5-HIAA excretion is usually elevated (1). In normal subjects, approximately 1% of dietary tryptophan is converted to serotonin (5-hydroxytryptamine), which is then metabolized to 5-HIAA (Figure 1). In patients with carcinoid syndrome, the conversion of tryptophan to serotonin can be

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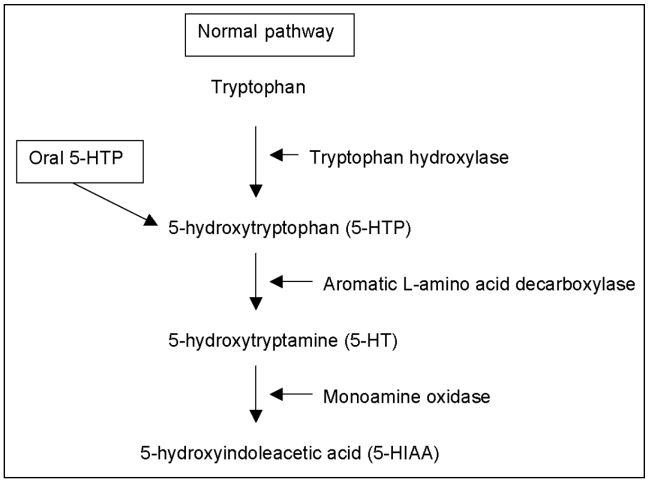

Figure 1) *Metabolism of tryptophan to 5-HIAA. Normally, conversion of tryptophan to 5-HIAA occurs through the intermediates of 5-HTP and 5-HT (serotonin). Oral ingestion of 5-HTP can enter the metabolic pathway for conversion by aromatic L-amino acid decarboxylase, with eventual production of 5-HIAA*

increased to approximately 70%, resulting in increased urinary 5-HIAA excretion. Urinary 5-HIAA levels can also be increased in malabsorption syndromes, such as celiac disease and Whipple's disease, as well as by ingestion of drugs and food that contain serotonin. Therefore, during urine collection to screen for carcinoid syndrome, patients are advised to adhere to a strict diet, avoiding products that alter 5-HIAA excretion (Table 1) (2). These problems with the use of urinary 5-HIAA for detection of carcinoid tumours have led to a search for other helpful markers of carcinoid tumours. Chromogranin A (CgA) has recently been introduced as a marker to confirm a clinical suspicion of neuroendocrine tumours, including carcinoid tumours (2). CgA is produced by a number of different neuroendocrine tumours, including pheochromocytomas, medullary thyroid carcinomas and carcinoid tumours, as well as by other tumours such as small cell lung cancer (3). Thus, although the specificity of CgA has been reported to be as high as 98% in those known to have carcinoid syndrome, the specificity of CgA in those suspected of having a carcinoid tumour can be much lower (4).

Recently, we examined a 77-year-old woman with an elevated 24 h urine 5-HIAA level of 510 µmol/day (normal levels less than 45 µmol/day), obtained as part of a workup for fatigue. She denied any symptoms of wheezing, flushing or diarrhea. Her medical history included glaucoma (treated with eye drops) and untreated mild hypertension. Physical examination was unremarkable except for a mildly elevated blood pressure of 148/96 mmHg. Her creatinine level was not elevated (67 µmol/L). During the urine collection to measure 5-HIAA level, she had strictly avoided food or drugs listed to interfere with 5-HIAA excretion. However, upon specific questioning, she informed us that during the urine collection, she had continued daily intake of 100 mg 5-hydroxytryptophan (5-HTP), obtained from a health food store, for insomnia until two weeks before being seen. In addition, the serum concentration of CgA was elevated at 72.1 U/L (normal levels less than 18 U/L). After discontinuation of 5-HTP, her 24 h urine 5-HIAA excretion normalized to 18 µmol/day and then increased to 314 µmol/day during a rechallenge with 5-HTP.

TABLE 1
Food and drugs that interfere with 24 h urine 5-hydroxyindoleacetic acid levels

Food	Products or drugs
Avocado	Acetaminophen
Bananas	Acetamilide
Kiwi	Caffeine
Pineapples	Chlorpromazine
Plums	Coumadin*
Tomatoes	Dextroamphetamine
Eggplant	Ephedrine
Pecans	Fluorouracil
Hickory nuts	Guaifenisin (Benylin†, Dimetapp‡)
Walnuts	Melatonin
Chocolate	Melphalan
Coffee and tea	5-aminosalicylic acid
Vanilla	Methocarbamol
Turkey	Naproxen
Cigarettes	Nicotine
	Phenobarbital
	Phenacetin
	Phenothiazine
	Reserpine
	Robitussin‡
	Ratio-Theo-Bronc§ (cough and cold medications)

**Manufactured by Bristol-Meyers Squibb, Canada; †Manufactured by McNeil Consumer Healthcare, Canada; ‡Manufactured by Wyeth Consumer Healthcare Inc, Canada; §Manufactured by Ratiopharm Inc, Canada*

One month after discontinuation of the 5-HTP, both her 24 h urine 5-HIAA level (35 µmol/day) and serum CgA level (6.7 U/L) had normalized.

The decision was made to determine whether, and to what extent, oral 5-HTP increases urine 5-HIAA excretion and serum CgA levels in healthy volunteers.

PATIENTS AND METHODS

Subjects

Eight healthy volunteers who were 18 years of age or older were recruited via local advertising. During a screening visit, medical history, current medications, blood pressure, heart rate, height and weight were documented. Subjects were excluded if they were pregnant, taking antidepressants or other drugs that affect 5-HIAA excretion in urine, or participating in other studies. All volunteers provided written, informed consent before inclusion. The study was approved in writing by the local ethics committee, conducted in accordance with the Declaration of Helsinki and registered at <www.clinicaltrials.gov> under study identification number NCT00227136.

Protocol

The study was performed in a single centre and followed a prospective, double-blind, placebo-controlled, randomized, crossover design with two treatment periods of 10 days each, separated by a washout period of at least four days. Capsules containing 100 mg 5-HTP (Wiler PCCA Fine Chemicals, Canada) and identical-looking capsules containing lactose

TABLE 2
Baseline characteristics of participants

Characteristic	Participants
Age, years, median (range)	38 (22–58)
Female/Male, n	5/3
Alcohol, units per week, median (range)	1.5 (0–12)
Median cigarettes per week, n	0
Body mass index, kg/m^2, median (range)	25 (22–38)
Systolic blood pressure, mmHg, median (range)	109 (92–128)
Diastolic blood pressure, mmHg, median (range)	70 (60–85)
Patients taking medication, n	
Multivitamins (not containing 5-HTP)	4
Proton pump inhibitor	1
Birth control pill	1
Other (nasal spray)	1

5-HTP 5-hydroxytryptophan

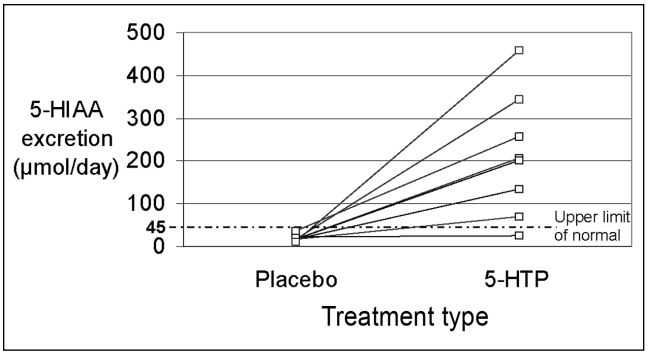

Figure 2) *Effect of 5-hydroxytryptophan (5-HTP) intake on urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion in individual participants. Placebo and 5-HTP results were obtained from urine collected after 10 days of placebo or 5-HTP intake (100 mg at bedtime). Other products affecting urinary 5-HIAA excretion were avoided during both urine collections.*

powder (Wiler PCCA Fine Chemicals) were prepared by the local pharmacy department, who also conducted computerized randomization (www.randomizer.org).

Volunteers were instructed to ingest the capsules each evening for 10 days, with placebo and 5-HTP intakes separated by a washout period of at least four days. From the morning of day 9 to the morning of day 11 of each period, the participants followed a specific diet that did not contain products that increase 5-HIAA excretion. On day 10 of each period, participants collected urine for 24 h in 2 L brown polypropylene bottles (containing 15 mL of hydrochloric acid 6N) for measurement of 5-HIAA and creatinine. On the morning of day 11, between 08:00 and 10:00, compliance was assessed by pill count. Participants were asked directly about any effects on sleep, mood or gastrointestinal symptoms. Any other side effects volunteered by participants were also documented. During that visit, 4 mL of blood was collected in a BD vacutainer tube (Becton Dickinson, Canada) containing 7.2 mg potassium EDTA for measurement of serum CgA. All samples were frozen at –80°C and batched for simultaneous laboratory determination.

All study personnel, lab personnel and volunteers were blinded to treatment assignments. The treatment allocation was unblinded after all study data were authorized and entered into the database.

Analytical methods

Urinary creatinine concentrations were analyzed on the Beckman Coulter LS-20 analyzer (Beckman Coulter Inc, Canada). Urinary 5-HIAA concentrations were determined using modified Bio-Rad high-pressure liquid chromatography kits (method 600-0087, Bio-Rad Laboratories, Germany). The extracts prepared by this method were analyzed by reverse phase column (Supelcosil LC-18 high-pressure liquid chromatography column, 3 µm particle size, 15 cm by 4.6 mm, Supelco, USA). The mobile phase purchased from Bio-Rad was run at a flow rate of 1.2 mL/min, with the column kept at an ambient temperature of 23°C. 5-HIAA levels were detected by the Coulochem III electrochemical detector for high-pressure liquid chromatography (ESA Biosciences, Inc) with the guard set at –420 mV and detector cell potentials at E1=50 mV and E2=370 mV. The between-run coefficients of variation were 6.31% and 5.37% at 5-HIAA levels of 23.8 µmol/L and 146.3 µmol/L, respectively.

Serum CgA levels were measured using a two-site immunometric assay (Dako, Denmark). Human CgA was used as a standard. Using a DSX open immunoassay analyzer (Dynex Technologies, USA), all samples were evaluated in duplicate in the same assay. The detection limit of the assay was 2.0 U/L. The between-run coefficients of variation were 10.78%, 3.6% and 5.8% at CgA levels of 14.8 U/L, 195.4 U/L and 364.0 U/L, respectively.

Statistical analysis

Results are presented as the median (range) unless otherwise indicated. Data were analyzed on a per protocol basis. Within-group comparisons were analyzed by Wilcoxon's signed rank test. $P<0.05$ was considered to be statistically significant. Based on the participation of eight subjects, the study design allowed for a 95% power to detect an increase of urinary 5-HIAA excretion of 30 µmol/day.

RESULTS

Baseline characteristics

Eight volunteers completed the study. Their clinical characteristics are shown in Table 2. Compliance (assessed by pill count) was 100% for all volunteers; no significant side effects were noted. One female participant had high CgA levels (184 U/L and 26 U/L) during placebo and 5-HTP intake, respectively. She was using a proton pump inhibitor (PPI), which may have increased her CgA levels. Her CgA level returned to normal (8.9 U/L) 30 days after discontinuation of the PPI. Therefore, her CgA data were not included in the analysis.

Effects of 5-HTP on urine 5-HIAA and serum CgA levels

Treatment with 5-HTP resulted in a 10-fold increase of 24 h urinary 5-HIAA levels, from 18 µmol/day (12 µmol/day to 36 µmol/day) during placebo intake to 204 µmol/day during 5-HTP intake (22 µmol/day to 459 µmol/day; P=0.017). 5-HIAA excretion varied considerably between individuals and was above the upper limit of normal in seven of the eight participants after 5-HTP ingestion (Figure 2). To correct for potential variation of sample collection, the ratio of

urine 5-HIAA to urine creatinine was calculated. This ratio increased from 1.4 µmol/day (0.9 µmol/day to 2.8 µmol/day) to 15.8 µmol/day (2.6 µmol/day to 40.0 µmol/day) during placebo and 5-HTP intake, respectively (P=0.012). 5-HTP administration did not affect serum CgA; levels were 6.2 U/L (4.2 U/L to 13.3 U/L) during placebo and 6.6 U/L (4.7 U/L to 12.6 U/L) during 5-HTP intake. 5-HTP intake did not result in significant beneficial effects on mood or sleep. No significant difference in adverse effects occurred between when participants were receiving 5-HTP and when they were receiving a placebo.

DISCUSSION

The present study demonstrates that oral intake of 5-HTP at a daily dose of 100 mg at bedtime results in a 10-fold increase in urinary 5-HIAA levels. It is critical to recognize nonprescription (over-the-counter) 5-HTP as a potential cause of increased 5-HIAA excretion, because oral ingestion of 5-HTP can easily enter into the pathway of 5-HIAA production (Figure 1). Falsely increased urinary 5-HIAA excretion may prompt costly further imaging studies in search of a carcinoid tumour and may be a source of unnecessary anxiety in patients. Further, although we did not measure the effect of 5-HTP in patients with documented carcinoid syndrome, we suggest that 5-HTP may also be a potential confounder when urinary 5-HIAA excretion is used to monitor these patients.

5-HTP can easily be obtained over-the-counter or via the Internet. 5-HTP is promoted as a harmless but essential amino acid that is necessary to sustain life, and that is beneficial for depression, anxiety, insomnia and obesity (5-10). The recommended dose varies from 50 mg to 1000 mg at bedtime; no data are available on the yearly sales volume (5-10). Patients often do not remember to inform their physicians of over-the-counter or herbal medications that they are taking. Further, physicians often fail to specifically ask about these preparations, especially because popular references such as <www.uptodate.com> or *Harrison's Principles of Internal Medicine* (11) do not list over-the-counter 5-HTP as a substance that can interfere with 24 h urine 5-HIAA levels.

Several studies have shown increased serotonin metabolite excretion in response to 5-HTP ingestion (12-14). In 1976, increases in the levels of plasma 5-HTP and plasma 5-HIAA were first documented in two healthy controls after 5-HTP administration (12). In open-label trials for depression, oral 5-HTP administration resulted in significant four- to 14-fold and eight- to 22-fold increases in mean urinary 5-HIAA excretion in controls and depressed patients, respectively (13,14). These studies did not always control for confounders such as dietary serotonin intake or other medications such as acetaminophen and phenothiazines, and the adequacy of urine collection (24 h urine creatinine) was not documented.

In our randomized, double-blind, placebo-controlled, crossover study, we found a similar 10-fold increase in 24 h urinary 5-HIAA excretion, with large interindividual variation. Similar results were found when results were corrected for 24 h creatinine excretion. Normalization of urinary 5-HIAA levels occurred within 14 days of stopping 5-HTP and may well have occurred sooner. A kinetics study of 5-HTP administration in healthy volunteers demonstrated a biological half-life of 2 h to 7 h and a plasma clearance rate (of plasma 5-HIAA) of 0.1 L/kg/h to 0.23 L/kg/h, thereby indicating rapid elimination (15). To our knowledge, no study has specifically examined the time period to normalization of urinary 5-HIAA levels after discontinuation of oral 5-HTP, although a parallel kinetic profile is expected.

Unfortunately, even though urinary 5-HIAA has been used as the initial biochemical test for patients suspected of having a carcinoid tumour, biochemical detection utilizing urinary 5-HIAA elevation is often fraught with errors. Urinary 5-HIAA levels may be increased in malabsorption syndromes, as well as after ingestion of certain drugs or food containing serotonin (2,16). As well, the sensitivity of 5-HIAA urinary level varies depending on the type of carcinoid being detected (17). In particular, foregut carcinoids can easily be missed if using urinary 5-HIAA levels alone to detect them, because foregut carcinoids often lack the L-amino acid decarboxylase activity required for conversion of 5-HTP to 5-HIAA (4). Thus, due to this low sensitivity, urinary 5-HIAA levels should only be tested in patients in whom carcinoid syndrome is truly suspected (unlike in our patient) and in whom appropriate instructions (of food and drugs to be avoided) for collection of urinary 5-HIAA have been given.

CgA has recently been introduced as a confirmation test for clinical suspicion of neuroendocrine tumours, including carcinoid tumours (2). While the specificity of CgA can be as high as 98% in patients with known carcinoid syndrome (4), less information is available on the use of CgA as a screening test for carcinoid syndrome. Our study indicates that oral 5-HTP intake does not increase serum CgA levels. Therefore, in patients unwilling to stop 5-HTP intake, CgA determination may be a useful alternative test.

One volunteer had an elevated CgA level that normalized after discontinuation of her PPI. Use of a PPI, even over the short term, can result in an average 1.5- to 2.5-fold increase in CgA levels, although a 13-fold increase in the CgA level in response to PPI intake has been described (18,19). Thus, CgA levels may be helpful in assessing for carcinoid tumours in patients taking 5-HTP, as long as the causes for falsely elevated CgA levels (ie, essential hypertension, hepatic failure, renal failure, PPI use, chronic atrophic gastritis) are remembered (18-21).

There were several limitations to our study. First, we studied the impact of only one 5-HTP dose (100 mg per day) on 5-HIAA excretion and therefore cannot comment on a potential dose-response relationship. However, even in this small group of eight volunteers, urinary 5-HIAA excretion in response to 5-HTP varied widely, from 22 µmol/day to 459 µmol/day, suggesting that interindividual differences in serotonin metabolism may cause large variations in 5-HIAA excretion. To our knowledge, only one other study (13) documented variations in urinary 5-HIAA in response to oral 5-HTP administration, but this study demonstrated large variations between depressed and nondepressed patients. This finding is plausible, because other studies have documented interindividual variations in plasma metabolite formation after oral 5-HTP intake (15,22). Second, our study included only a small number of participants, and we did not include patients with documented carcinoid syndrome, in whom altered serotonin metabolism may change the magnitude of the effect of oral 5-HTP on 5-HIAA excretion and/or symptoms. Third, our study did not assess the impact of oral 5-HTP ingestion on 5-HTP and 5-HIAA levels in plasma. Recent studies have proposed the use of plasma platelet 5-HTP or plasma 5-HIAA levels as more convenient or better screening tests for the diagnosis of carcinoid syndrome (23,24). An open-label trial (13) of 150 mg 5-HTP daily for

seven days demonstrated variable changes (from a 25% decrease to a 75% increase) in plasma 5-HTP levels and a 33% to 60% increase in plasma 5-HIAA levels. Further studies may need to assess the impact of oral 5-HTP intake on plasma 5-HTP and plasma 5-HIAA levels.

Our index patient had an elevated CgA level that normalized one month after discontinuation of 5-HTP ingestion. This finding was not supported by the results of our crossover trial in healthy volunteers. Although she did have mild hypertension, her blood pressure had not improved enough in her follow-up visit to account for her improvement in CgA levels. Moreover, no other non-neoplastic causes of elevated CgA levels were found to contribute to her elevation in CgA level. Unfortunately, she declined to undergo further imaging studies. One year later, she is free of symptoms, but we cannot completely exclude the presence of a carcinoid tumour.

CONCLUSIONS

5-HTP supplementation can falsely elevate urinary 5-HIAA levels but not serum CgA levels, thereby leading to a false diagnosis of carcinoid syndrome. The use of over-the-counter 5-HTP should be excluded as the cause of increased urinary 5-HIAA levels before initiating diagnostic tests to search for a carcinoid tumour. This may avoid unnecessary psychological anxiety and expense. Popular reference sources should add 5-HTP as a substance that may cause increased urinary 5-HIAA levels.

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