

Association between Urinary Neurotransmitter Status and Scoliosis Progression: A Case-Controlled Series

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Abstract

Previous investigations into the relationship between neurotransmitter abnormalities and idiopathic scoliosis have been mixed. The purpose of the present study was to evaluate the differences in a urinary neurotransmitter profile across three different groups. These groups included a progressive scoliosis group, a non-progressive scoliosis group, and a non-scoliotic control group. When evaluating urinary neurotransmitter levels across all groups, statistically significant differences were observed between all three groups for multiple neurotransmitters. The differences seemed to increase as the scoliosis increased in Cobb angle measurement. Further studies should seek to distinguish a potential cause or effect relationship between these neurotransmitter abnormalities and idiopathic scoliosis onset and/or progression.

Keywords

Histamine, Neurotransmitters, Norepinephrine, Scoliosis, Serotonin

1. Introduction

Scoliosis is a condition characterized by a curvature of the spine that exceeds 10° as measured by Cobb's angle on radiographic examination [1]. Although scoliosis has been historically viewed as a purely biomechanical disorder, recent investigations into its underlying causes have led to metabolically-driven etiological models [2]. Investigation into the relationship of various neurotransmitters and idiopathic scoliosis has been extensive in recent decades. The most com-

monly studied neurotransmitter relative to scoliosis is melatonin. Much of this work was published in the mid-1990s, when Machida *et al.* showed that melatonin deficiency in pinealectomized chickens may cause idiopathic scoliosis [1]. This theory was additionally tested on rats and hamsters in a 1999 study by O'Kelly *et al.* [3]. Around this same time period, studies involving human subjects were also published, with mixed results. A small case-controlled series was published by Hillibrand *et al.* [4] comparing 9 females with scoliosis to 18 females without. Daytime and nighttime urinary melatonin via liquid chromatography showed no difference in melatonin levels between the two groups. Additional studies by Bagnall *et al.* [5] and Fagan *et al.* [6] failed to identify a relationship between melatonin deficiency and idiopathic scoliosis. Although frank melatonin deficiency could not be connected to idiopathic scoliosis in humans, researchers have offered alternative explanations for scoliosis and melatonin. Moreau *et al.* found that melatonin signaling dysfunctions may exist in the osteoblasts of patients with idiopathic scoliosis [7]. Wu *et al.* found that asymmetric melatonin receptor expression in the paravertebral muscles may play a role in the onset of idiopathic scoliosis [8]. Additional studies in melatonin signaling dysfunction [9] and abnormal paravertebral melatonin receptor expression [10] support these theories of scoliosis onset as compared to melatonin deficiency.

Aside from melatonin, serotonin has also been implicated in idiopathic scoliosis. Machida *et al.* [11], in another study of pinealectomized chickens, gave a cohort of these chickens intraperitoneal injections of 5-hydroxytryptophan (5-HTP), the precursor to serotonin. These pinealectomized chickens did not develop idiopathic scoliosis. Serotonin is chiefly responsible for memory consolidation with the central nervous system, including long-term postural motor memory [12]. In the CNS, serotonin is chiefly produced in the raphe nuclei. Axons from the lower raphe nuclei communicate with the cerebellum and spinal cord [13]. Peripherally, alterations in serotonin levels have been associated with altered bone metabolism [14] and gastrointestinal dysfunction [15].

Histamine is also an important neurotransmitter involved in many central and peripheral pathways. Centrally, histamine is an important regulator of the pathways responsible for kinematic postural stability [16], as well as the modulation of neuroplastic changes from novel activities [17]. To date, no studies have identified any link between scoliosis and peripheral or central histamine levels.

Glutamate is the chief excitatory neurotransmitter, and most abundant free amino acid in the central nervous system [18]. Glutamate is primarily responsible for neural plasticity, and regulates it via N-Methyl-D-Aspartate (NMDA) acid receptor activity. NMDA receptor stimulation results in long-term potentiation, which facilitates new motor learning and memory networks [19] [20].

Norepinephrine functions to modulate cortical plasticity, through its activation of the locus ceruleus [21]. Activation of the locus ceruleus results in accelerated perceptual learning [22], as well as the maintenance or increase in synapse strength [23].

Previous observational studies have shown that patients with idiopathic scoliosis may display abnormal levels or ratios of these neurotransmitters compared to non-scoliotics [24], and that improving these imbalances may contribute to increased benefit from conservative scoliosis treatment [25]. The purpose of the present study was to expand upon the observations of previous studies on neurotransmitters and scoliosis. The authors hypothesize that scoliotic curves that are more progressive may show different neurotransmitter patterns than in patients who have more stable scoliotic patients, as well as compared to non-scoliotic patients.

2. Methods

Patient records from 2 different medical clinics in Pennsylvania and Michigan were pulled and evaluated from a pool of patients attending these two clinics in 2016-2017. Patient charts were included for study if they met the following inclusion criteria: 1) patient had a history of idiopathic scoliosis (juvenile or adolescent), 2) patient completed at least one urinary neurotransmitter test, 3) the patient had been followed through Risser 4. Using these inclusion criteria, a total of 105 patient files were collected and analyzed. All patient records that fit the inclusion criteria were included in the sample group. After this aggregate of patient files were collected, a second collection was performed. In this instance, patient charts were pulled if they did not have idiopathic scoliosis, and also had completed at least one neurotransmitter test. These patients were being managed for other diagnoses. This collection of charts served as the control group. Once both groups of charts were identified, the scoliosis group of charts were further subcategorized into the two following groups: 1) if the patient had a curve measuring greater than 50° prior to end of growth, and 2) those whose curves were stable and did not reach 50° by end of growth. All patients whose charts were selected provided their written informed consent to publish their non-identifying data. When all of the patient records had been identified, the neurotransmitter test results were pulled from each file and tabulated. Based upon previous observations by Morningstar [24], urinary levels of serotonin, histamine, norepinephrine, and glutamate were collected and averaged among all three groups. The levels of each of these neurotransmitters were compared to the other groups.

A power analysis was conducted for each neurotransmitter using an online calculator (<http://www.sample-size.net>). For serotonin, the minimum sample size required for 80% power to show a 47 µg/g difference was 39 patients in each of the scoliosis groups. The minimum sample size for 80% power for comparison between the non-progressive and non-scoliotic serotonin levels was 49 patients. The sample size required for histamine comparisons between the 2 scoliosis groups, as well as the non-progressive and non-scoliotic groups, were 37 patients and 63 patients, respectively. Finally, the minimum sample sizes for norepinephrine were 21 patients for the scoliosis groups' comparison, and 53 patients

for the non-progressive/non-scoliotic groups' comparison.

3. Results

A total of 52 patients (50 female, 2 male) were included in the group with progressive idiopathic scoliosis. Their average age was 11 years, 7 months, with a range of 9 years 3 months to 43 years, 10 months. In this group, the average serotonin level was $127 \mu\text{g/g} \pm 66$. The average glutamate level was $50 \mu\text{mol/g} \pm 26$, while histamine was $26 \mu\text{g/g} \pm 12$, and norepinephrine was $67 \mu\text{g/g} \pm 11$. The non-progressive idiopathic scoliosis group was comprised of 53 patients (49 female, 4 male), with an average age of 13 years 4 months, ranging from 10 years, 6 months to 25 years, 5 months. Their average neurotransmitter levels were as follows: serotonin was $170 \mu\text{g/g} \pm 71$, glutamate was $49 \mu\text{mol/g} \pm 30$, histamine was $32 \mu\text{g/g} \pm 14$, and norepinephrine was $57 \mu\text{g/g} \pm 24$. For the non-scoliosis patient group, there were 82 patients total (73 female, 9 male) that were included for analysis. Their average age was 24 years, 1 month, with a range of 14 years, 9 months to 51 years, 8 months. Serotonin levels in this group averaged $190 \mu\text{g/g} \pm 35$, glutamate averaged $44 \mu\text{mol/g} \pm 10$, histamine was $39 \mu\text{g/g} \pm 9$, and norepinephrine averaged $48 \mu\text{g/g} \pm 20$. One-way ANOVA testing using each neurotransmitter as the independent variable showed that serotonin, norepinephrine, and histamine levels were statistically significantly different among the 3 groups ($P < 0.001$). Differences in glutamate levels between the 3 groups did not reach statistical significance ($P = 0.338582$). **Figure 1** provides a comparative view of the neurotransmitter levels among the 3 patient groups.

All 3 groups were also compared to one another using 2-tailed paired t-tests. **Table 1** shows a comparison of the t-test results. When comparing the progressive scoliosis group with the non-progressive scoliosis group, the progressive group had statistically significantly lower levels of serotonin and histamine; with elevated norepinephrine. Glutamate was not different between the groups. When

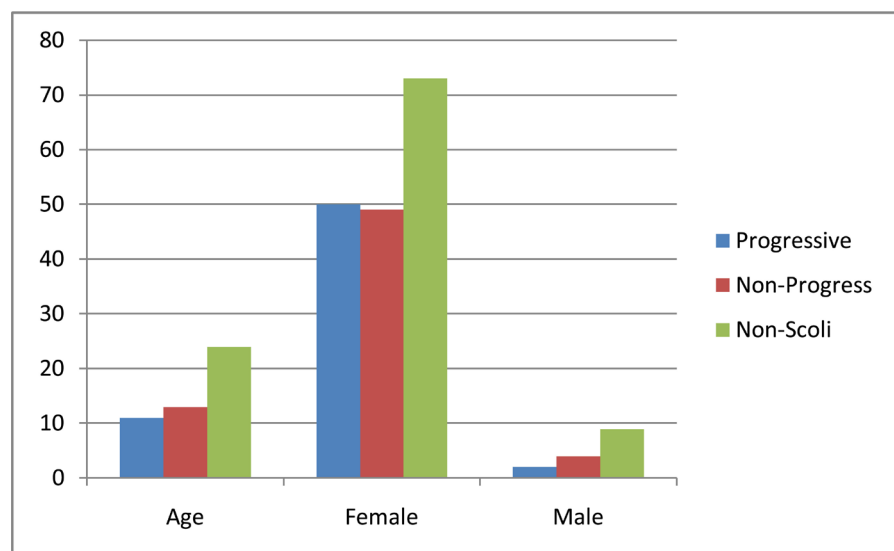


Figure 1. Demographic information for each group.

Table 1. Results of t-test comparisons between all groups.

Neurotransmitter	T-Test Comparisons		
	P-NP ^a	P-NS ^b	NP-NS ^c
Serotonin	0.0009456*	3.034E-08*	0.0316477*
Glutamate	0.462012	0.1545891	0.2408662
Histamine	0.0258175*	2.844E-09*	0.0018546*
Norepinephrine	0.037042315*	4.85187E-08*	0.007690843*

^aProgressive vs. Non-Progressive; ^bProgressive vs. Non-Scoliotic; ^cNon-Progressive vs. Non-Scoliotic; *Statistically significant at $P < 0.05$.

the progressive scoliosis group was compared to the non-scoliosis group, the same neurotransmitters were statistically significant, but with larger differentials for each neurotransmitter. The non-progressive scoliosis group was also compared to the non-scoliosis group. In this instance, the non-progressive scoliosis group also had statistically significant differences between serotonin, histamine, and norepinephrine, although they did not reach the same level of difference as when the progressive scoliosis group was compared to the non-scoliotic group.

4. Discussion

Interestingly, serotonin, norepinephrine, and histamine fibers all have concentrations in the raphe nuclei, the cerebellum, and the vestibular system. Given the unique importance of these centers on reflexive neuromotor spinal control [24], disturbances in the levels of these neurotransmitters may have significant effects on spinal neuromotor output. This is supported by a previous study in which patients who participated in a chiropractic rehabilitation treatment for idiopathic scoliosis, and who also received concurrent treatment for urinary neurotransmitter imbalances, reported better follow-up outcomes at 6 months compared with patients who did not receive the neurotransmitter portion of treatment [25] [26].

As the demand for more conservative scoliosis treatments increases, it will become desirable to develop strategies to predict any given patient's potential response to therapy. In observing the differences in the peripheral urinary neurotransmitters in the present 3 groups of patients, testing such as this may help determine which patients may be considered for therapy, while identifying those at high risk for progression. Those at high risk may be referred for surgical consultations and potential intervention in a more proactive perspective.

It is important to discuss the limitations of the present study. Selection bias cannot be discounted due to study design. Also, there is some debate over the reliability and validity of urinary neurotransmitter testing [27]. However, previous studies on urinary neurotransmitter testing have shown associations between peripheral neurotransmitter measurements and central neurotransmitter function and symptoms [28] [29]. More investigation needs to take place in this regard to further identify the connections between peripheral urinary neurotransmitter

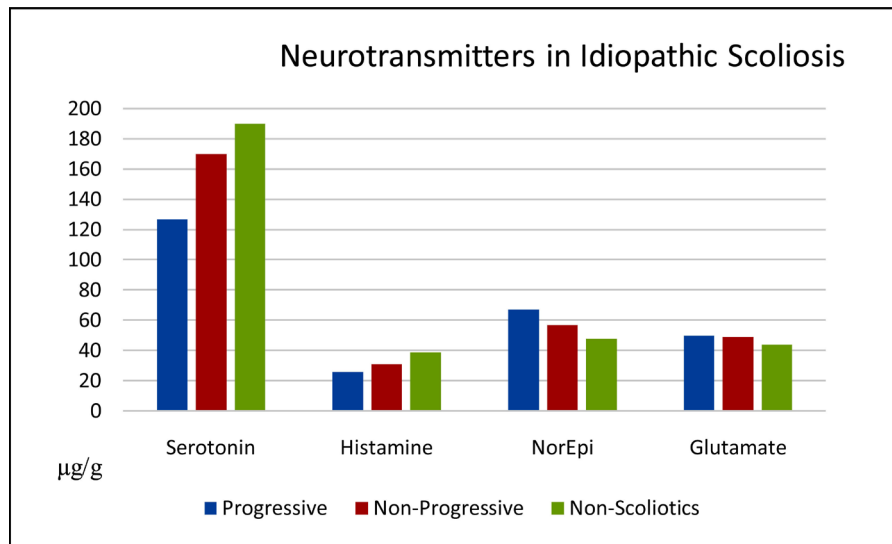


Figure 2. Neurotransmitter levels in all groups.

levels and central nervous system function. Finally, the type II error for the t-test significance between the histamine levels of the non-progressive group and the non-scoliotic group could not be ruled out due to the fact that the sample size did not meet the minimum 80% power calculation. Therefore, no conclusions can be made for this particular intergroup comparison (**Figure 2**).

5. Conclusion

When comparing the urinary neurotransmitter levels between 3 groups of patients, patients with a scoliosis beyond 50° had statistically significantly different levels of serotonin, histamine, and norepinephrine, when compared to patients with scoliosis below 50°, as well as comparing with patients without a history of idiopathic scoliosis. Patients with idiopathic scoliosis below 50° had a statistically significant difference in their serotonin and norepinephrine levels when compared to non-scoliotics. Although these differences have been observed, the manner in which these observed differences influence scoliosis is presently unknown. Further studies should investigate the type of influence these observed differences have on idiopathic scoliosis, such as causative or progressive.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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