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Genetic Study of Neuropeptide W Gene Expression in Children with Short Stature

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ABSTRACT

Background: Short stature in children is a multifactorial condition with both environmental and genetic determinants. Neuropeptide W (NPW) is a bioactive peptide that plays a role in neuroendocrine regulation and growth hormone secretion.
Aim: This study aimed to assess the role of NPW gene expression in the pathogenesis of short stature in children.
Patients and methods: This cross-sectional study included 100 children with short stature (aged 2–18 years) attending the Pediatric Endocrinology Outpatient Clinic, Menoufia University Hospitals, and 80 apparently healthy age- and sex-matched controls. All participants underwent detailed history taking, anthropometric measurements, clinical examination, and laboratory investigations, including genetic mRNA expression analysis of NPW.
Results: A highly significant increase in NPW mRNA expression was observed in patients compared to controls ($p < 0.001$), with a 1.022-fold elevation in patients. No significant association was found between NPW expression levels and demographic variables such as sex or age. **Conclusion:** NPW gene overexpression may contribute to the development of short stature, possibly through modulation of the growth hormone axis. Further research was needed to confirm these findings and explore potential therapeutic implications.
Keywords: Neuropeptide W, Short stature, Gene expression, Pediatric endocrinology, mRNA.

INTRODUCTION

Short stature is characterized by a standing height that falls more than two standard deviations below the average expected for an individual's age and sex. Its etiology is heterogeneous, involving genetic, endocrine, nutritional, and chronic disease-related causes. The growth hormone (GH) axis plays a critical role in determining final adult height, and its regulation is influenced by several neuropeptides [1]. Neuropeptide W (NPW) is a small bioactive peptide encoded by the preproprotein L8 gene. It is involved in multiple physiological processes, including energy homeostasis, stress response, and modulation of hypothalamic-pituitary function. Animal studies have suggested that NPW stimulates GH release, but its role in human growth disorders remains under investigation [2].

This study aimed to evaluate NPW mRNA expression levels in children with short stature and assess their potential role in growth impairment.

PATIENTS AND METHODS

Study Design:

This cross-sectional study was conducted at the Pediatric Endocrinology Outpatient Clinic, Menoufia University Hospitals.

Participants:

Cases: 100 children (2–18 years) with short stature (height > 2 SD below the mean for age and sex). **Controls:** 80 age- and sex-matched apparently healthy children.

Inclusion Criteria: Both sexes.
Age between 2 and 18 years.
Short stature as defined above.

Exclusion Criteria:

Autoimmune disorders (e.g., diabetes mellitus, thyroid dysfunction, celiac disease).
Chronic cardiovascular, respiratory, or urinary diseases.
Known genetic syndromes (e.g., Down syndrome, Turner's syndrome).

Procedures:

1. **History Taking:** Personal, medical, drug, and family history, including pedigree analysis.
2. **Clinical Examination:** General and systemic examination, anthropometric measurements, mid-parental height calculation, and pubertal assessment (Tanner staging).
3. **Genetic Analysis:** mRNA expression quantification by RT-PCR

Ethical Approval: Written informed consent was obtained from all participants before enrolment. Approval for the study protocol was granted by The Local Ethical Research Committee of Menoufia Faculty of Medicine, as well as the Institutional Review Board. The research procedures adhered to the principles outlined in the Declaration of Helsinki and its subsequent revisions.

Statistical Analysis

Data processing was performed with SPSS version 25. Continuous data were summarized as mean ± standard deviation, while categorical data were presented as frequencies and percentages. Group comparisons were carried out using Student's *t*-test for continuous variables and the Chi-square test for categorical variables. Statistical significance was set at $p \leq 0.05$.

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RESULTS

Comparison of Sociodemographic data between the studied groups shows no significant differences between patients and controls regarding age, sex, birth order, or consanguinity. A significant difference was observed only in maternal age, (p=0.015, 0.035).

Table (1): Comparison of Sociodemographic data between the studied groups

	Patients (n = 100)		**Controls (n = 100)**		**Test of Sig.**	**p**
Age (years)						
Min. – Max.	4.0 – 16.0		4.0 – 16.0		U= 4466.0	0.189
Sex						
Male	47	47.0	52	52.0	χ^2= 0.500	0.479
Female	53	53.0	48	48.0		
Birth order						
1	44	44.0	38	38.0	χ^2= 4.496	0.213
2	36	36.0	34	34.0		
3	16	16.0	16	16.0		
≥4	4	4.0	12	12.0		
Consanguinity						
No	93	93.0	90	90.0	χ^2= 0.579	0.447
Yes	7	7.0	10	10.0		
Maternal age (in years)						
Min. – Max.	18.0 – 33.0		18.0 – 35.0		U= 4007.5*	0.015*
<20 years	15	15.0	7	7.0	χ^2= 6.684*	0.035*
20 – 30 years	82	82.0	83	83.0		
>30 years	3	3.0	10	10.0		

SD: Standard deviation U: Mann Whitney test χ^2: Chi square test.

p: p value for comparing between Patients and Controls *: Statistically significant at p ≤ 0.05

Comparison between patients and controls according to anthropometric measurements demonstrates that patients had significantly lower weight, height, arm span, and both upper and lower segment measurements compared to controls (p<0.001). No significant differences were observed regarding head circumference or upper/lower segment ratio.

Table (2): Comparison between patients and controls according to anthropometric measurements

	Patients (n = 100)	**Controls (n = 100)**	**Test of Sig.**	**p**
Weight (kg)			U= 2170.50*	<0.001*
Min. – Max.	12.0 – 60.0	17.0 – 60.0		
Height (cm)			U= 1645.50*	<0.001*
Min. – Max.	89.0 – 155.0	109.0 – 171.0		
Head circumference (cm)			t= 1.050	0.295
Min. – Max.	49.0 – 55.0	50.0 – 54.0		
Arm spam (cm)			U= 1816.0*	<0.001*
Min. – Max.	87.0 – 157.0	107.5 – 172.0		
Upper SEG (cm)			U= 1606.0*	<0.001*
Min. – Max.	45.0 – 78.0	56.0 – 84.0		
Lower SEG (cm)			U= 1867.0*	<0.001*
Min. – Max.	43.0 – 80.0	53.0 – 87.0		
U\L Segment Ratio			t= 1.389	0.167
Min. – Max.	0.911 – 1.120	0.920 – 1.110		

t: Student t-test, U: Mann Whitney test, p: p value for comparing between Patients and Controls, *: Statistically significant at p ≤0.05

mRNA Expression: NPW expression was significantly higher in patients with short stature compared to controls ($p < 0.001$), with a 1.022-fold increase (Table 3).

Table (3): Comparison between patients and controls according to genes expressions.

	Cases (n = 100)	Controls® (n = 100)	p	OR (95% C.I)
NPW				
Mean ± SD.	69.0 ± 129.8	12.56 ± 17.60	<0.001*	1.022 (1.011 – 1.034)

OR: Odd's ratio, ®: Reference group , CI: Confidence interval
p: p value for Univariate regression analysis.

Demographic Associations: NPW expression levels showed no significant correlation with age, sex, or family history of short stature.

DISCUSSION

The present study demonstrated a significant overexpression of NPW mRNA in children with short stature compared to healthy controls. This suggests a possible role for NPW in growth regulation, potentially via the GH axis.

Prior experimental studies provide a basis for interpreting our findings. Neuropeptide W (NPW) acts centrally through its receptors—GPR7 (NPBWR1) and GPR8 (NPBWR2)—affecting neuroendocrine outputs such as GH, prolactin, and corticosterone [3]. Notably, intracerebroventricular administration of NPW-23 in male rats suppressed circulating GH levels while elevating prolactin and corticosterone [5].. Studies in birds further corroborate that NPW directly inhibits GH (and prolactin) release from the pituitary [6].These data suggest that NPW may act as an inhibitory modulator of GH secretion via hypothalamic–pituitary pathways.

Additionally, more recent mechanistic insight shows that the central effects of NPW inhibiting GH release involve activation of arcuate somatostatin neurons [7]. Though human data remain limited, these recent findings strengthen the proposed inhibitory role of NPW in GH regulation.

Our observation of increased NPW expression in children with short stature aligns with these findings—suggesting that elevated NPW may either represent a compensatory up-regulation in response to diminished GH activity, or indicate dysregulated hypothalamic–pituitary control contributing to growth.

However, the absence of a significant association between NPW expression and specific demographic or clinical variables suggests that NPW's role in short stature may be independent of these factors.

CONCLUSION

NPW gene expression was significantly elevated in children with short stature. This finding supports the hypothesis that NPW plays a role in human growth regulation. Larger-scale and longitudinal studies are needed to confirm causality and clarify clinical implications. Further research is required to elucidate the mechanisms linking NPW to growth regulation and to explore whether targeting NPW pathways could have therapeutic potential.

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