# Does prenatal testosterone have a role in development of cerebral palsy?

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**Abstract**

**Introduction:** Cerebral palsy occurs in about 2 – 2.5 per 1000 live births (1). The cause of cerebral palsy is unknown. Prenatal events are responsible for approximately 75 % of all the cases of Cerebral palsy.

**Aim:** To determine the influence of testosterone on development of cerebral palsy.

**Materials and Methods**: 51 cerebral palsy children, 29 boys and 22 girls in age group of 7- 12 years participated in the study. Age matched healthy children (29 boys and 25 girls) formed the control group. The right and left hands of cerebral palsy children and controls were scanned. The lengths of second digit and fourth digit were measured and ratio of second to fourth digit was calculated.

**Results**: The results show lower 2D:4D values in boys compared to girls in control group ($P< 0.05$). No significant difference was found in 2D:4D ratio between cerebral palsy group and control group in boys and girls.

**Conclusion**: Present study indicates that pre natal testosterone exposure does not influence the development of cerebral palsy.

**Key words**: 2D:4D, brain development, cerebral palsy, prenatal testosterone.

## Introduction

Cerebral palsy occurs in about 2 – 2.5 per 1000 live births (1). The cause of cerebral palsy is unknown. Prenatal events are responsible for approximately 75 % of all the cases of Cerebral palsy. Possible causes include brain malformations (2,3), maternal infections (4), vascular events, metabolic conditions (5) & toxins (6).Hormones are known to play an important role in development of brain. Children with cerebral palsy have poor linear growth during childhood with short final height. Studies have shown a prevalence of growth hormone deficiency in children with cerebral palsy (7). Thyroid hormone deficiency is also known to be related to cerebral palsy. Premature infants with transient hypothyroxemia have elevated risks of cerebral palsy. Studies of the antecedents of cerebral palsy have encountered a higher than expected prevalence of maternal thyroid disorders (8). Corticosteroid therapy for treating chronic lung disease may increase the infants risk for cerebral palsy (9). Neonatal interferons exceeding control concentrations were associated with other biochemical and clinical indicators of inflammation and with spastic diplegia (10).Sex hormones, particularly testosterone is considered to be crucial in the development of brain (11). Cerebral palsy and related developmental disorders are more common in males than females. Experimental studies in animals and data from adult patients with stroke indicate that sex hormones such as estrogens provide protection against hypoxic ischemic injury (12). Increased fetal testosterone levels are found in children with autistic traits (13). Studies have not been done to determine the potential role of prenatal testosterone in development of cerebral palsy. Estimation of serum hormone levels in the fetal period is a difficult and risky procedure (14). Researchers have used indirect methods of measuring prenatal hormone exposure to study effects on later development. One such indirect measure is the ratio between the length of the second and fourth digits (2D:4D) of the hand. This ratio has been found to be sexually dimorphic, being lower in males than in females (15). The 2D:4D ratio is

thought to be fixed by week 14 of foetal life, and has been found to reflect foetal exposure to prenatal sex hormones in early gestation (16).

**Aim**

In the present study we examined a retrospective marker of prenatal testosterone exposure – 2D:4D finger length ratio, the relative length of 2nd and 4th digit in 51 cerebral palsy children and 54 age and sex matched controls.

**Material and Methods**

The study was conducted at Mobility India, an NGO in Bangalore which provides rehabilitation intervention for cerebral palsy patients. The study was approved by institutional ethical committee. A written informed consent was obtained from parents of all the children. 51 cerebral palsy children, 29 boys and 22 girls in age group of 7- 12 years participated in the study. 54 age matched healthy children (29 boys & 25 girls) formed the control group. Both the hands of participants were scanned with a HP scanjet scanner. Participants placed their relaxed hands slightly on the surface of the scanner with second to fifth fingers held parallel and the tip of the middle finger aligned with the wrist and elbow. Scanned hand images were scaled and later printed by a HP LaserJet printer. Measurements of second and fourth fingers (in mm) were taken from printouts with the use of vernier calipers (Quasmo – Range 0 – 150 mm, accuracy ± 0.05 mm). These measurements were taken from the tip of the finger to the basal crease. Where two creases were visible at the base of the digit the proximal crease was chosen. A single reader conducted all the measurements. The 2D:4D was calculated as the length of the second digit divided by the length of the fourth digit.

**Statistical Analysis**

Data obtained in this study was analyzed statistically by computing descriptive statistics like mean, standard deviation & 95 % confidence interval for mean. The difference in means between study and control groups were tested statistically using student's t-test. The difference was considered statistically significant whenever $P \leq 0.05$. SPSS V.11.0 was used for analysis of data.

**Results**

This study indicate that the ratio of second to fourth digit is lower in boys compared to girls in control group both in right and left hands (Table 1). No significant difference was found in 2D:4D Ratio of both hands between cerebral palsy group and control group in boys (Table 2). Similar results were found in girls with no significant difference in 2D:4D Ratio of both hands between cerebral palsy group and control group (Table 3).

**Table 1** – Comparison of 2D:4D ratio of right & left hands in boys & girls controls.

| | | | | 95% Confidence Interval for Mean | | | |
|---|---|---|---|---|---|---|---|
| | | N | Mean ± SD | Lower Bound | Upper Bound | t-value | p-value (two-tailed |
| 2D:4D Right | Male control | 29 | 0.9426 ± 0.0303 | 0.9310 | 0.9541 | 2.751 | 0.008 |
| | Female control | 25 | 0.9636 ± 0.0050 | 0.9532 | 0.9740 | | |
| 2D:4D Left | Male control | 29 | 0.9405 ± 0.0317 | 0.9284 | 0.9525 | 2.084 | 0.042 |
| | Female control | 25 | 0.9636 ± 0.0224 | 0.8623 | 0.9910 | | |

**Table 2** –2D:4D ratio of right & left hands in cerebral palsy boys compared with their controls.

| | | | | 95% Confidence Interval for Mean | | | |
|---|---|---|---|---|---|---|---|
| | | N | Mean ± SD | Lower Bound | Upper Bound | t-value | p-value (two-tailed |
| 2D:4D Right | Cerebral Palsy | 29 | 0.9515 ± 0.0449 | 0.9344 | 0.9685 | 0.887 | 0.379 |
| | control | 29 | 0.9426 ± 0.0303 | 0.9310 | 0.9541 | | |
| 2D:4D Left | Cerebral Palsy | 29 | 0.9390 ± 0.0339 | 0.9261 | 0.9519 | 0.172 | 0.864 |
| | control | 29 | 0.9405 ± 0.0317 | 0.9284 | 0.9525 | | |

**Table 3** – 2D:4D ratio of right & left hands in cerebral palsy girls compared with their controls.

| | | | | 95% Confidence Interval for Mean | | | |
|---|---|---|---|---|---|---|---|
| | | N | Mean ± SD | Lower Bound | Upper Bound | t-value | p-value (two-tailed |
| 2D:4D Right | Cerebral Palsy | 22 | 0.9499 ± 0.0302 | 0.9365 | 0.9633 | 1.699 | 0.096 |
| | control | 25 | 0.9636 ± 0.0252 | 0.9532 | 0.9740 | | |
| 2D:4D Left | Cerebral Palsy | 22 | 0.9521 ± 0.0283 | 0.9396 | 0.9647 | 0.558 | 0.581 |
| | control | 25 | 0.9636 ± 0.0224 | 0.8623 | 0.9910 | | |

## Discussion

The ratio of second to fourth finger length (2D:4D index) has been intensively studied during the recent few years (17, 18, 19). This index is lower in men than in women and varies also within sexes. Sex differences in 2D:4D develop in prenatal period (20) and remain stable across the life span (21) of an individual. Earlier studies have indicated that the relative length of 2$^{nd}$ to 4$^{th}$ digit (2D:4D) is related to prenatal sex hormones with low 2D:4D associated with exposure to higher concentration of prenatal testosterone than estrogen (22, 23). 2D:4D ratio is therefore used as a tool to investigate possible associations between prenatal sex hormone exposure and various disorders (24, 25, 26). Testosterone is an important hormone in the development of the brain. Direct measurement of this hormone prenatally is difficult and hence 2D:4D ratio measurement gives an indirect evidence of prenatal exposure to testosterone. Cerebral palsy is a common disorder involving the brain and its cause is still not clearly established. Various hormones like growth hormone, thyroid hormones and corticosteroids are known to be associated with cerebral palsy. Therefore it is plausible that testosterone may have a role in development of cerebral palsy. The results show a significant difference in the second to fourth digit ratio between boys and girls among the control group with boys having a lower 2D:4D ratio than girls in both right and left hands. This is in accordance to various studies done earlier which show a significantly lower 2D:4D ratio in males compared to females. The result of our study does not show any significant difference in the 2D:4D ratios between

cerebral palsy children and control groups both in right and left hands. The results are similar among both boys and girls.

## Conclusion

To conclude, present study indicates that pre natal testosterone exposure does not influence the development of cerebral palsy. This study clearly establishes that testosterone is a non-causative factor in development of cerebral palsy.

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