

Evaluation of Autonomic Nervous System in Children With Cerebral Palsy: Clinical and Electrophysiological Study

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Abstract

Cerebral palsy (CP) is the most prevalent severe motor disability among children. The aim of this work was to assess autonomic dysfunction in children with cerebral palsy clinically and electrophysiologically. The study was carried out on forty children with cerebral palsy their age ranged from 4-12 years and twenty healthy children with matched age and sex as control group. CP children were subjected to questionnaire for autonomic dysfunction symptoms. Both CP children and Control group were assessed for Sympathetic Skin Response and Heart rate variability. Most of children had quadriplegic spastic cerebral palsy (82.5%). Based on Gross motor function classification system (GMFCS) classification the majority of children were in levels 4 and 5. The prevalence of autonomic dysfunction symptoms was 80% for thermoregulatory abnormalities (cold extremities), chronic constipation 65%, sleep disturbance 52.5%, loss of appetite 47.5%, sweating abnormalities 40% , recurrent nausea and/or vomiting 25%, increased sensitivity to light or dark 22.5% and bloating 15%. The percentage of unelicited Sympathetic skin response in CP children was 47.5% and 60% in upper limbs and lower limbs respectively, all of them were in level 4 and 5 of GMFCS. 20% of CP children had postural hypotension. Mean Heart rate of CP children was significantly increased more than healthy children upon head tilt test. Sympathetic Skin Response and Heart rate variability were proven to be simple and non invasive procedures in investigating autonomic dysfunction in CP children.

Introduction

Cerebral palsy (CP) is the commonest cause of motor disability in childhood (Cans et al. 2008; Himmelman et al. 2009). It has been described as "A group of disorders of the development of movement and posture causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain (Novak et al . 2017).

The autonomic nervous system (ANS) is made up of pathways of neurons that control various organ systems inside the body through chemicals and signals to maintain homeostasis. It consists of the sympathetic and parasympathetic systems. The sympathetic component is better known as "fight or flight" and the parasympathetic component as "rest and digest." It functions without conscious control throughout the lifespan of an organism to control cardiac muscle, smooth muscle, and exocrine and endocrine glands, which in turn regulate blood pressure, urination, bowel movements, and thermoregulation (Mc Corry 2007) . Despite Autonomic Dysfunction being very common and severely affecting the quality of life of CP children, there has been virtually few research in this area at all. So the aim of this work was to assess autonomic dysfunction in children with cerebral palsy clinically and electro-physiologically and to relate the results to the level of motor impairment as classified by the Gross Motor Function Classification System.

SUBJECTS :

The study was carried out on sixty children divided into two groups:

Group I: forty children with spastic cerebral palsy. They were selected from those attending the outpatient Neurology Clinic and Physical Medicine, Rheumatology and Rehabilitation Clinic of Alexandria University Children's Hospital at El Shatby.

Group II: twenty healthy children of matched age and sex as a control group for sympathetic skin response and Heart rate variability.

We excluded children with any cardiac pathology which may affect heart rate. Also children taking medication known to influence autonomic nervous system as β blocker and antiepileptic drugs were excluded

The study was explained to the participants and their parents and an informed consent was taken from parents of all children included in the study.

Methods

Group I was subjected to:

1-Thorough history taking include history of any symptoms of autonomic dysfunction (Suarez et al. 1999) through questionnaire directed to the parents consists of 8 items:

Thermoregulatory (2 items): cold extremities and sweating abnormalities.

Gastro-intestinal (4 items): loss of appetite, bloating, chronic constipation and recurrent nausea and/ or vomiting (N&V),Pupillo-motor (1 item): increased sensitivity to light and Sleep disturbances (1 item)

2-Blood pressure was measured in supine position and 90° head up position either by standing or passively holding the child in upright position to assess presence of postural hypotension (Freeman et al. 2011).

Postural hypotension: reduction of systolic blood pressure at least 20 mmHg or diastolic pressure 10 mmHg within 3 minutes of standing or passive head up tilt (Freeman et al. 2011 ; Shalem et al. 2013).

3-Complete neurological examination included (Swaiman et al. 2006):

- Mental state, posture, cranial nerves examination, motor system examination; muscle strength, tone, bulk and reflexes, and sensory system examination.

4- Assessment of function by Gross motor function classification system (GMFCS) (Palisano et al. 2006).

Both groups were assessed for:

I .Sympathetic skin response (Dettmers et al. 1993; Gutrecht 1994)

II . Heart rate variability (European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996)

I ..Sympathetic skin response (Dettmers et al. 1993; Gutrecht 1994).

a) Sympathetic skin response of the upper limb:

The stimulating electrode was placed on the median nerve at the wrist, cathode is directed distally, the nerve is stimulated on the same side of recording. The recording electrodes were placed so the active electrode was put on the palmar aspect of the hand and the reference electrode was put on the dorsum of the hand. The ground electrode was placed at the wrist region.

Stimulation parameters: electric stimulation used. Frequency 0.1 HZ, sharp square impulse of 0.2 mSec duration with current intensity of 10-30 mA. Analysis time 5 sec and vertical gain ranged from 5-100 uV/division.

Filter setting: low cut 20 HZ, high cut 3 KHZ.

With repetitive stimulation, the inter-stimulus interval should not be more frequent than 1 per minute to minimize the phenomenon of habituation.

b) Sympathetic skin response of the lower limb:

The stimulating electrode was placed on the posterior tibial nerve above and posterior to the medial malleolus, cathode is directed distally, the nerve is stimulated on the same side of recording. The recording electrodes were placed so the active electrode was put on the plantar aspect of the foot and the reference electrode was put on the dorsum of the foot. The ground electrode was placed at the ankle region. Stimulation parameters: electric stimulation used. Frequency 0.1 HZ, sharp square impulse of 0.2 mSec duration with current intensity of 10-30 mA. Analysis time 10 sec and vertical gain ranged from 5-100 uV/division. Filter setting: low cut 20 HZ, high cut 3 KHZ. With repetitive stimulation, the inter-stimulus interval should not be more frequent than 1 per minute to minimize the phenomenon of habituation.

The following parameters were assessed for sympathetic skin response (Elie, Guiheneuc 1990)

1-Onset latency in seconds (sec.): measured from stimulus artifact to the first deflection from base line.

2-Amplitude in microvolt (μV): measured from the peak of the first deflection to the peak of the next one (peak to peak)

At least 3 trials were carried out before we considered the response to be absent

For diagnosis of autonomic neuropathy by sympathetic skin response, we consider abnormal SSR if there is absence of SSR (Vetrungo et al 2003) .

II. Heart rate variability (European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996)

- Heart rate variability through 12 lead ECG with long strip lead II in both supine & in 90° head up positions after 10 minutes of active standing or passively by holding the child in upright position.
- Each QRS complex in long lead II strip was detected and the so called R-R intervals (RRI) (that is all intervals between adjacent QRS complexes resulting from sinus node depolarizations) were calculated.
- Time domain measures that were calculated included the mean R-R interval, the mean heart rate.

Orthostatic tachycardia: in pediatric age is defined as a rise in heart rate for at least 40 beats/minute or heart rate more than 130 beats /minute within 10 minutes of active standing or passive head-up tilt (Freeman et al 2011; Singer et al 2012).

Postural orthostatic tachycardia syndrome (POTS): is characterized by orthostatic tachycardia without orthostatic hypotension and may be accompanied by symptoms of orthostatic intolerance (Freeman et al 2011).

Statistical analysis of the data (Kirkpatrick, Feeney 2013) :

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution . Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level.

Results

In the current study, males constituted 60%, while females constituted 40% of the total number of both CP children and healthy children. The mean age of CP children was 7.76 ± 2.82 years (ranged from 4 years to 12 years) with no statistical difference between CP children and healthy children regarding age.

Regarding cause of CP among studied group: in 80% of the children the cause was Perinatal, in 12.5% it was postnatal and prenatal in 7.5% of the cases.

82.5% of the studied group were quadriplegic and 17.5% were diplegic. Based on GMFCS, most of CP children were in levels 4 (45%) and level 5 (37.5%) .Only 12.5% of children were in level 2 and 5% were in level 3.

The most encountered symptom of autonomic dysfunction was cold extremities in 80% of the cases, followed by chronic constipation in 65%, then sleep disturbances in 52.5%, then loss of appetite in 47.5%, sweating abnormalities in 40%, recurrent nausea and/or vomiting (N&V) in 25% , increased sensitivity to light in 22.5%, and the least encountered symptom was bloating in 15% .

The percentage of un-elicited SSR in CP children was 47.5% in upper limbs (ULs) and 60% in lower limbs (LLs).

All healthy children in the control group had elicited SSR. Regarding the results of elicited SSR among CP children, the mean latency of upper limbs was 1.11 ± 0.23 sec and the mean amplitude was 64.44 ± 27.07 μ V. The mean latency for lower limbs was 1.51 ± 0.45 sec and mean amplitude was 62.53 ± 23.59 μ V. There was no significant difference between elicited SSR among CP children and healthy children.

AS the number of cases with unelicited SSR LLs was more than the number of cases with unelicited SSR ULs so we considered the number of cases with unelicited SSR LLs more appropriate as a presentative of the total number of cases with unelicited SSR as it includes unelicited SSR both limbs and unelicited SSR lower limbs. All autonomic dysfunction symptoms were more common in children with unelicited SSR than children with elicited SSR with statistical significance as regard cold extremities, chronic constipation, sleep disturbances and sweating abnormalities. (Table 1)

Table 1 Relation between SSR LLs with autonomic dysfunction symptoms

| Autonomic dysfunction symptoms | SSR LLs | | | | c ² | P |
|--------------------------------|---------------------|------|-------------------|-------|----------------|-------------------------|
| | Unelicited (n = 24) | | Elicited (n = 16) | | | |
| | No. | % | No. | % | | |
| Cold extremities | 22 | 91.7 | 10 | 62.5 | 5.104* | FE _p =0.042* |
| Sweating abnormalities | | | | | | |
| Increased (hyperhidrosis) | 4 | 40.0 | 6 | 100.0 | 5.760* | FE _p =0.034* |
| Decreased (hypohidrosis) | 6 | 60.0 | 0 | 0.0 | | |
| Loss of appetite | 13 | 54.2 | 6 | 37.5 | 1.069 | 0.301 |
| Bloating | 5 | 20.8 | 1 | 6.3 | 1.601 | FE _p =0.373 |
| Chronic Constipation | 20 | 83.3 | 6 | 37.5 | 8.864* | 0.003* |
| Recurrent N&/V | 8 | 33.3 | 2 | 12.5 | 2.222 | FE _p = 0.263 |
| Increased sensitivity to light | 6 | 25.0 | 3 | 18.8 | 0.215 | FE _p = 0.717 |
| Sleep disturbances | 17 | 70.8 | 4 | 25.0 | 8.087* | 0.004* |

c2: chi square test

fe: fisher exact

*: statistically significant at $p \leq 0.05$

The mean heart rate (HR) of CP children in supine position was 100.83 ± 15.28 beats/minute with mean R-R interval (RRI) 0.60 ± 0.10 sec, and the mean HR in 90 degrees head up position was 115.18 ± 19.77 beats/minute with mean RRI 0.54 ± 0.10 sec. The mean heart rate of healthy children in supine position was 98.15 ± 8.93 beats/minute with mean RRI 0.61 ± 0.06 sec, and the mean HR in 90 degrees head up position was 103.80 ± 8.58 beats/minute with mean RRI 0.58 ± 0.06 sec. There was significant difference between HR and RRI between the two positions in the two groups, $P < 0.001$ in both groups.

There was no significant difference between two groups regarding supine mean HR and mean RRI but there was significant difference between two groups regarding mean HR and mean RRI in 90 degrees head up position, (Table2).

Table 2 Comparison between the two studied groups according to HRV

| | HRV | CP children (n = 40) | Healthy children (n = 20) | t | P |
|--------------------|-------------------|-------------------------|------------------------------|--------|--------|
| Supine | Mean HR(beat/min) | | | | |
| | Min. – Max. | 76.0 – 136.0 | 78.0 – 107.0 | 0.854 | 0.397 |
| | Mean \pm SD. | 100.83 ± 15.28 | 98.15 ± 8.93 | | |
| | Median | 103.0 | 101.50 | | |
| | Mean RRI(sec) | | | | |
| | Min. – Max. | 0.44 – 0.78 | 0.56 – 0.76 | 0.448 | 0.656 |
| | Mean \pm SD. | 0.60 ± 0.10 | 0.61 ± 0.06 | | |
| | Median | 0.58 | 0.59 | | |
| 90 degrees head up | Mean HR(beat/min) | | | | |
| | Min. – Max. | 76.0 – 166.0 | 80.0 – 111.0 | 3.102* | 0.003* |
| | Mean \pm SD. | 115.18 ± 19.77 | 103.80 ± 8.58 | | |
| | Median | 118.0 | 107.0 | | |
| | Mean RRI(sec) | | | | |
| | Min. – Max. | 0.36 – 0.79 | 0.53 – 0.74 | 2.018* | 0.048* |
| | Mean \pm SD. | 0.54 ± 0.10 | 0.58 ± 0.06 | | |
| | Median | 0.51 | 0.56 | | |

t: student t-test

*: statistically significant at $p \leq 0.05$

p: p value for comparing between the two groups

35% of CP children had orthostatic tachycardia. Of them 20% of CP children had orthostatic tachycardia with postural hypotension while 15% of them without postural hypotension. (Figure 1)

ALL CP children with orthostatic tachycardia had unelicited SSR except 2 had elicited SSR.

Table 3 Relation between GMFCS with SSR and Orthostatic tachycardia

| | GMFCS | | | | | | | | c ² | MC _p |
|-------------------------|--------------|-------|--------------|-------|---------------|------|---------------|------|----------------|-----------------|
| | 2 (n = 5) | | 3 (n = 2) | | 4 (n = 18) | | 5 (n = 15) | | | |
| | No. | % | No. | % | No. | % | No. | % | | |
| UL | | | | | | | | | | |
| Un-elicited | 0 | 0.0 | 0 | 0.0 | 11 | 61.1 | 8 | 53.3 | 7.367* | 0.035* |
| Elicited | 5 | 100.0 | 2 | 100.0 | 7 | 38.9 | 7 | 46.7 | | |
| LL | | | | | | | | | | |
| Un-elicited | 0 | 0.0 | 0 | 0.0 | 13 | 72.2 | 11 | 73.3 | 11.734* | 0.003* |
| Elicited | 5 | 100.0 | 2 | 100.0 | 5 | 27.8 | 4 | 26.7 | | |
| Orthostatic tachycardia | 1 | 20.0 | 0 | 0.0 | 8 | 44.4 | 5 | 33.3 | 1.845 | 0.673 |

c²: chi square test

MC: monte carlo

*: statistically significant at $p \leq 0.05$

All the children with unelicited SSR were in levels 4 and 5. No children in levels 2 or 3 had unelicited SSR.

Regarding the relation between orthostatic tachycardia and GMFCS, only one affected child was in GMFCS level 2 and the rest of affected children were in levels 4 and 5 (Table3).

Discussion

Sympathetic skin response is a simple, quick, easy applicable and non-invasive test that is frequently used in clinical neurophysiology laboratories to evaluate ANS (Elie, Guiheneuc 1990).

Although amplitude of SSR seems to be more sensitive parameter for detection of autonomic dysfunction, Some authors considered only unelicited response to be regarded as abnormal duo to the high variability of amplitude and habituation phenomenon of SSR (Kucera P 2004).

Autonomic neuropathy was reported in this study electrophysiologically by unelicited SSR only as there was no significant difference between elicited SSR among CP children and healthy control children.

Sympathetic skin response in CP children showed considerable percentage of unelicited responses, as 47.5% of the studied children had unelicited response in upper limbs and 60% had unelicited response in lower limbs, all of them were in level 4 and 5 of GMFCS.

These results are in agreement with previous study (Ogawa A et al 2007) which demonstrated that all children with severe motor and intellectual disabilities had unelicited SSR and the cases with mild to moderate severity had elicited responses.

But inconsistent with other study (Yang et al 1997) which demonstrated no significant difference between their studied CP children and healthy controls regarding SSR as the authors didn't enroll in their study children with severe quadriplegia in the contrary to current study as the majority of the studied children were quadriplegic in levels 4 and 5 of GMFCS.

Significance of autonomic dysfunction in children with unelicited SSR than in children with elicited SSR indicates that these symptoms are correlated to autonomic dysfunction proved by unelicited SSR.

Most of our patients were in grade 4 & 5 GMFCS this is explained by the high prevalence of quadriplegic type -the most severe type of cerebral palsy- among the studied group as Alexandria university children hospital is a tertiary center so more severe cases were referred to it.

Postural hypotension was assessed through blood pressure examination in supine and 90° head up position. 20% of CP children had Postural hypotension.

In healthy individuals; if the blood pressure falls upon standing, the baroreceptors which are located in the walls of the highly elastic great vessels, send fewer signals so parasympathetic activity decreases, allowing the heart rate to rise. More important, sympathetic neural impulse activity increases and causes stimulation of the rate and contractility of the heart, and constriction of arteriolar and venous blood vessels. These effects serve to reverse the drop of blood pressure (Reichgott M 1990).

In individuals having Postural hypotension; it is ascribed to defective increase in arterial resistance and excessive venous pooling upon standing or passive head up position (Weiling W et al 2004). It may be attributed to imbalance between sympathetic and parasympathetic systems (Reichgott M 1990).

Regarding HRV: CP children showed higher supine mean HR than healthy children but with no significant difference between them. This result is compatible with park et al study and Ferriera et al study, both studies demonstrated non-significant increase in resting mean HR in CP children than healthy children (park et al 2002 and Ferriera et al 2011). Yet, it was inconsistent with Yang et al study which showed significant increased resting HR in CP children than healthy children. It was measured in relaxing

sitting position and they attributed their result to increased energy consumption in CP children even upon sitting (Yang et al 1997).

Both CP children group and control group showed significantly increased mean HR in 90° head up position than supine position. This is compatible with a study which demonstrated significantly increased mean heart rate in CP individuals during orthostatic test (kerppers et al 2009). On the other hand park et al study showed incompatible results to the present study regarding effect of orthostatic test among CP children as it showed no significant difference in mean HR between two positions on CP children unlike the result of test among their healthy children which demonstrated significantly increased mean heart rate upon orthostatic stress. Park used 70° head up position but it is not stressful as 90° head up position in this young age group (park et al 2002).

The present study also showed significant difference between CP children and control group regarding mean HR during head up position which reflects that mean HR of CP children was markedly increased more than healthy children upon head up position.

Normally, during standing or head up position, vasovagal withdrawal and sympathetic predominance occur resulting in increase of heart rate and contractility(Reichgott M 1990) , this explains increased mean HR in healthy children during orthostatic stress.

35% of CP children showed excessive increase of heart rate in head up position meeting the definition of orthostatic tachycardia which is considered one of manifestations of autonomic dysfunction. Orthostatic tachycardia occurs due to failure of peripheral vasculature to vasoconstrict appropriately during upright position leading to excessive increase in heart rate and contractility to maintain blood pressure in relatively normal levels. This mechanism may not be fully compensatory in cases had both orthostatic tachycardia and postural hypotension (low P et al 1994).

Orthostatic tachycardia is found more among cases with unelicited SSR and GMFCS levels 4 and 5 suggesting that cases with severe cerebral palsy are more prone to autonomic dysfunction.

15% of CP children had orthostatic tachycardia not associated with postural hypotension. Postural orthostatic tachycardia syndrome (POTS) may be suggested in these children (Freeman R et al 2011). It is considered a milder form of dysautonomia, and explained by relatively intact sympathetic arteriolar function with selectively impaired sympathetic venomotor function (Weiling et al 2004).

Autonomic dysfunction is objectively proved in CP children through absent SSR, presence of orthostatic tachycardia and postural hypotension and both are attributed to sympatho-vagal imbalance.

Limitation of the present work

- It was inapplicable to assess all symptoms of autonomic dysfunction in CP children as most of children couldn't express themselves.

- The objective assessment of the clinical autonomic symptoms might provide a better analysis of the relationship with SSR and HRV results.
- It was better to assess HRV through frequency domain which can differentiate between sympathetic cardiovascular dysfunction and parasympathetic dysfunction and assess sympathovagal imbalance more appropriately but it was not available.

Declarations

Ethical approval : All procedures completed in the study involving human participants were in agreement with the ethical standards of the institutional research committee (Medical Research Ethics Committee of Alexandria Faculty of Medicine, Egypt) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Consent to participate : The study was explained to the participants and their parents and an informed consent was taken from parents of all children included in the study

Consent for publication: all authors accepted publication of this research

Conflict of interest: The authors declare that they have no conflict of interest

Availability of data and materials: patients were selected from those attending the outpatient Neurology Clinic and Physical Medicine, Rheumatology and Rehabilitation Clinic of Alexandria University Children's Hospital at El Shatby .Twenty healthy children of matched age and sex as a control group for sympathetic skin response and Heart rate variability

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Figures

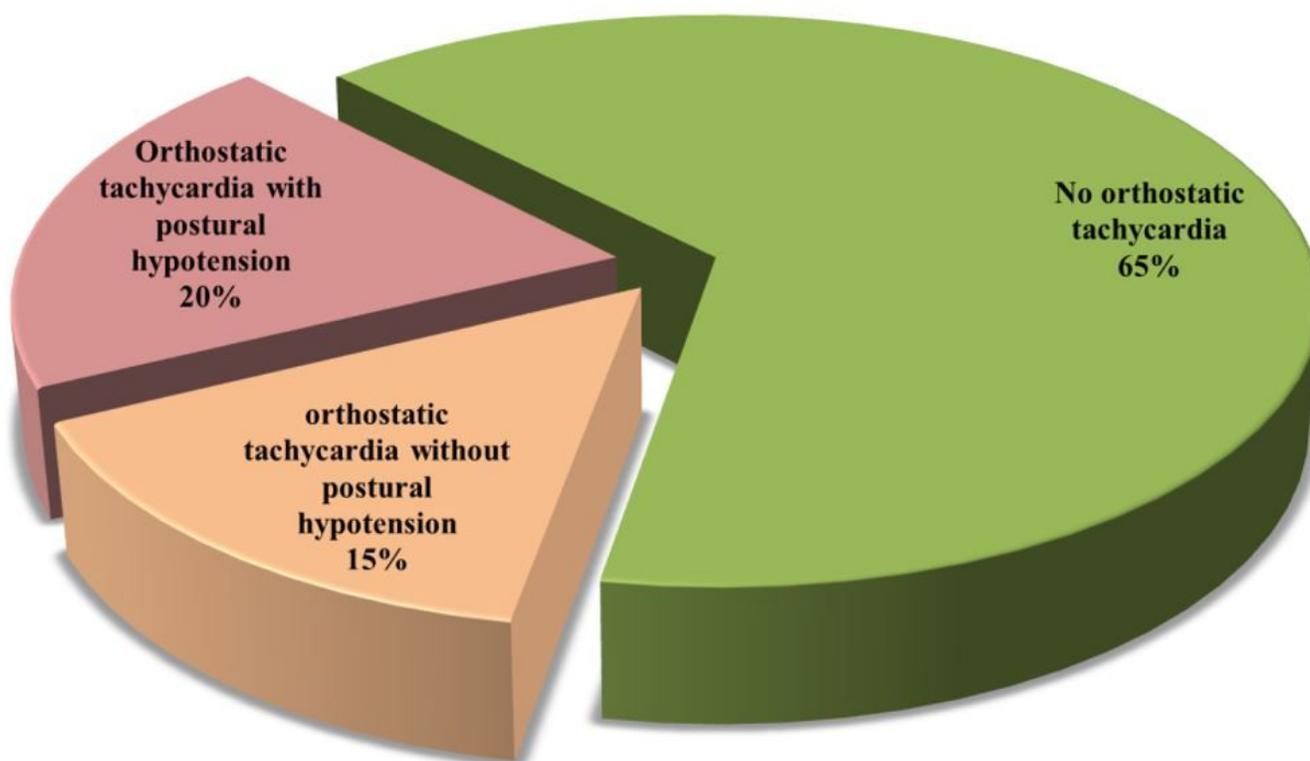


Figure 1

Distribution of the CP children according to presence of orthostatic tachycardia and postural hypotension (n = 40)