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Autonomic Dysfunction in Pediatric Patients with Previous COVID-19 Infection and Cardiovascular Affection

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Abstract

Background: Limited studies exist on autonomic dysfunction associated with long-COVID. The most common are orthostatic intolerance (OI) and postural orthostatic tachycardia syndrome (POTS).

Aim of Study: To evaluate autonomic dysfunction as POTS & OH in children 12 months after previous COVID 19 infectionat the cardiology unit, children's hospital, Ain Shams University.

Patients and Methods: This was a cross-sectional study that included 25 children aged from six to sixteen years who had a history of past COVID infection. They were subjected to tilt table test the period from June to November 2023. Theirclinical data were collected, includingtheir anthropometric measures, vital data, echocardiography, covid serology and tilt table test results.

Results: Our patients included males (68.0%) compared to females (32.0%). Tachycardia was evident in 20% of the patients indicating an abnormally elevated heart rate of more than 40 bpm in response to change in position from supine to incline. None of the patients exhibited abnormal significant decreases in systolic or diastolic blood pressure. Meanwhile, there was a significant change in heart rate in relation to the systolic and the diastolic blood pressure, *p*-value was 0.026 and 0.000 respectively.

Conclusion: Postural Orthostatic Tachycardia Syndrome appears to be associated with Post COVID-19 syndrome.

Key Words: Past-COVID infection – Pediatric – Cardiovascular – Autonomic dysfunction – POTS – OH – Tilt Table Testing.

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Introduction

POST-COVID is a heterogenous multisystem condition which does not yet have a precise definition. It includes signs and symptoms that persist after SARS-CoV-2 infection. This includes ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more) **[1].** Some of the long-COVID symptoms appear to be autonomic in nature. This includes orthostatic intolerance, tachycardia, syncope, orthostatic hypertension, fatigue and exercise intolerance **[2].**

The most common autonomic diagnoses associated with long-COVID are orthostatic intolerance (OI) and postural orthostatic tachycardia syndrome (POTS) **[2].** Patients with POTS and OH experience cardiac symptoms (e.g., palpitations, chest pain, dyspnea, and exercise intolerance) and/or noncardiac symptoms (e.g., mental clouding/"brain fog," headaches, lightheadedness, fatigue, muscle weakness, gastrointestinal symptoms, sleep disturbances, and chronic pain) symptoms, all of which reduce daily functional capacity. Currently, the pathophysiology is not well-understood. Physical deconditioning, hypovolemia, and immunological mechanisms are among the factors contributing to symptoms **[3].**

A recent hypothesis is that long COVID symptoms could be attributed to dysautonomia. Dysautonomia can be defined as malfunction of the autonomic nervous system (ANS), and it can be acute or chronic and progressive or reversible. Many symptoms can manifest from dysautonomia, including fatigue, heart rate variability (HRV) dysfunction and orthostatic hypotension. The most prevalent cardiovascular dysautonomia amongst young people is postural orthostatic tachycardia syndrome (POTS) **[4].**

Despite the prevalence of prolonged symptoms and emerging data on various manifestations, lim-

ited studies exist and primarily focuses on adult populations with limited information on pediatric populations **[5]**.

The aim of this study is to evaluate the presence of autonomic using tilt table test in patients aged six to sixteen years with past Covid 19 infection-at the Pediatric Cardiology unit of Children's Hospital, Ain Shams University in the duration from 1/6/2023 to 30/11/2023.

Patients and Methods

Study design:

This was an observational cross-sectional study evaluating the presence of orthostatic hypotension and postural orthostatic tachycardia syndrome using tilt table test. The study included 25 pediatric patients who had a history of past COVID infection six to twelve months before the study.

Patients with Congenital heart disease, Central Nervous System disease, recent history of infection, surgery, or concussion were excluded.

History taking included time of COVID infection, symptoms during COVID infection and disease severity, residual symptoms; palpitation, exercise intolerance and syncope.

General examination includedtheir weight and height measurement with z-score were calculated. Local examination of different body systems was done to assess the presence of any residual complications of multisystem inflammatory syndrome.

Regarding the tilt table test, subjects were kept supine on the tilt bed for more than ten minutes Meanwhile, their heart rate, blood pressure, and electrocardiogram were monitored and recorded. After recording the baseline vital data of the subject in the prone position, the subject was tilted 60° with the head high and feet in low position for 15 seconds. Vital data was initially, during the tilt and at the time point of a positive response. Collected data underwent statistical analysis to determine the presence of autonomic dysfunction in these patients as chronic symptoms.

POTS was diagnosed when orthostatic heart rate increment was more than or equals 40 bpm compared with the supine position or an absolute orthostatic heart rate more than or equals 130 bpm for children 12 years and younger or more than or equals 125 bpm for adolescents 13–18 years during tilt table test, with a BP decrease less than 20/10 mmHg. Orthostatic Hypotension is described as a steady decrease in BP exceeding 20mmHg systolic or 10mmHg diastolic within 3 minutes of standing from supine.

Ethical consideration: The study started after acquiring ethical approval from Research Ethics Committee of Ain Shams University. An informed consent was also be obtained from care givers.

Statistical analysis: SPSS (statistical package for social sciences) was used for data management and data analysis. Mean ± standard deviation described quantitative variables and median with interquartile range when appropriate (distribution deviated from normality).

Number and percentages described qualitative data and Chi-square or / Fisher exact tested proportion independence. For comparing mean values of two independent groups, parametric or non-parametric *t*-tests were used. For comparing mean values of more than two groups, one way ANOVA test was used. A post-hoc Turkey Honest Significant Different (HSD) test was done if ANOVA test showed an overall significant difference between the groups to determine where the significance lies. Differences were considered significant if the *p*-value was less than 0.05.

Results

All the involved 25 patients had post COVID-cardiac manifestations, 23 patients were diagnosed as Multisystem Inflammatory Syndrome in Children (MIS-C) (92.0%) and 2 patients with Post COVID Kawasaki (8.0%).

The mean age of the study group was 9.98±3.17 years ranging from 6 to 15.75 years. Males were predominant accounting for 17 (68.0%) of the patients compared to 8 (32.0%) females. No medical co-morbidities were encountered.

Symptom analysis showed fever asthe most common symptom followed by abdominal pain (100.0% & 80.0% respectively) which are often associated with Multisystem Inflammatory Syndrome in Children (MIS-C). Loss of smell and taste (8.0%) were reported in a small minority of patients.

The most frequently reported residual symptoms were headache (32.0%) followed by fatigue and dizziness (20.0%) after standing among the studied patients.

Left ventricular dilatation with impaired function was identified in eight patients (32.0%). Eighteen patients (72.0%) required mechanical ventilation while twenty patients (80.0%) required admission to the Pediatric Intensive Care Unit (PICU). All were discharged after improvement.

During Tilt Table Test most of the patients had normal baseline heart rate, systolic blood pressure and diastolic blood pressure. One patient, who was tachycardic throughout the test. She had been on Carvedilol due to Sinus Tachycardic. This was confirmed through electrocardiogram. Change in heart

rate from supine to inclineposition was the only statistically significant finding (p<0.001), indicating a substantial increase in heart rate. (Table 1).

Postural Orthostatic Tachycardia Syndrome was significantly associated with palpitations (p<0.01). It also had high association with residual symptoms such as dyspnea on exertion, fatigue after standing, headache & dizziness on standing (p=0.003,0.000, 0.010, 0.000 respectively).

In incline position systolic blood pressure was significantly associated with residual symptoms fatigue & dizziness after standing (p=0.012) as well as left ventricular dilatationa previously recorded finding during their hospital stay (p=0.027).

Diastolic Blood Pressurewas also significantly associated with residual symptoms fatigue and dizziness after standing (p=0.005).

Furthermore, a significant decrease was noticed insystolic blood pressure (p=0.026, S) as well as diastolic blood pressure (p=0.000, HS) between patients with postural orthostatic tachycardia syndrome and those without. This decrease was not more than 20mmHg in SBP nor 10mmHg in DBP. (Table 2).

Table (1): Comparison between vital data in Supine position and Incline position among the studied patients in tilt table test.

	Supine	Incline	% of change Median (IQR)	Test value	*p*-value	Sig.
Heart Rate						
Bpm:						
Mean ± SD	85.44±16.42	104.6±9.24	25 (6.25 – 36.49)	–6.592•	<0.001	HS
Range	60 – 125	90 – 120				
SBP mmHg:						
Mean ± SD	112.2±13.33	115.2±17.64	0.83 (-2.08 – 6.42)	–1.570•	0.130	NS
Range	92 – 150	91 – 166				
DBP mmHg:						
Mean ± SD	66.04±9.15	67.88±11.02	5.26 (-4.84 – 8.96)	–1.433•	0.165	NS
Range	49 – 93	41 – 89				

p-value >0.05: Non-significant. *p*-value <0.01: Highly significant.
p-value <0.05: Significant. •: Paired *t*-test.

Table (2): Relation of presence of Postural Orthostatic Tachycardia Syndrome with vital data at supine and incline among the studied patients.

	HR (>=40 BPM		Test value	*p*-value	Sig.
	Normal No.=20	POTS No.=5			
Supine					
SBP:			1.628•	0.117	NS
Mean ± SD	114.30±13.84	103.80±6.80			
Range	92 – 150	96 – 111			
DBP:			1.186•	0.111	NS
Mean ± SD	67.90±8.97	58.60±5.81			
Range	54 – 93	49 – 64			
Incline			2.386•	0.026	S
SBP:			4.230•	0.000	HS
Mean ± SD	119.05±17.36	99.80±8.14			
Range	91 – 166	92 – 110			
DBP:					
Mean ± SD	71.45±8.46	53.60±8.35			
Range	52 – 89	41 – 63			

p-value >0.05: Non-significant. *p*-value <0.01: Highly significant.
p-value <0.05: Significant. •: Independent *t*-test.

Discussion

The term post-acute sequelae of SARS-CoV-2 infectionis used to describe the persistence of symptoms or development of sequelae beyond three weeks from the onset of acute symptoms. Research shows that it affects the cardiovascular system because of autonomic nervous system dysfunction as sequalae *[6,7]*.

Ormiston et al., stated that excessive bed rest, night sweats, fever, and nausea typically accompany SARS-CoV-2 infection and may interact synergistically in patients with post-acute sequalae of Covid 19 to later cause hypovolemia, baroreflex dysfunction, diminished cardiac output, and cardiac sympathetic nervous system activation. These symptoms can lead to physical deconditioning and ultimately postural orthostatic tachycardia syndrome *[8]*.

This observational cross-sectional study was conducted on 25 patients aged from six to sixteen years with a history of past COVID-19 infection confirmed by positive PCR or IgG serology and cardiovascular complications related to COVID-19 admitted to Pediatric Cardiology Unit, Children's hospital, Ain Shams University from June 2023 to November 2023.

Similar to our study, Feldstein et al., showed that children were predominantly males (68.0%) with mean age approximately 9.98 years. Also, in line with the current study, Khoury et al., enrolled 1767 children and revealed that there were 338 (21.6%) with and 1429 (78.4%) with MIS-C. This means that MIS-C has a higher incidence than Kawasaki Disease although each within a certain age group. *[9,10,11]*.

A systematic review and meta-analysis by Hoste et al., showed that multisystem inflammatory syndrome post covid was characterized by fever (99.4%), gastrointestinal (85.6%) and cardiocirculatory manifestations (79.3%) and increased inflammatory biomarkers similar to this study *[12]*.

Asadi-Pooya et al., reported twenty-six (44·8%) children/adolescents with symptoms/complaints of long COVID. These symptoms included fatigue in 12 (21%), shortness of breath in 7 (12%), exercise intolerance in 7 (12%), weakness in 6 (10%), and walking intolerance in 5 (9%) individuals also in line with the current study *[13]*.

Dufort et al. showed that 79 patients with post COVID MIS-C (80%) were admitted to an intensive care unitand 10 (10%) required mechanical ventilation similar to ourstudy. Also, in line with Ergenc et al., results, none of the patients had documented comorbidities and all of them improved after the initial period of infection *[14,15]*.

The proportion of patients with positive SARS-CoV-2 serology testing was substantially greater than of those with positive SARS-CoV-2 RT-PCR tests. These findings as well as increased markers of hyperinflammation are consistent with the hypothesis that MIS-C results from a post infectious inflammatory process *[10]*.

Huang et al. and Carfi et al., observed that Covid-19 related cardiac symptoms such as chest pain, heart palpitation, and tachycardia have continued up to 6 months among Covid-19 survivors indicating that long-term cardiac symptoms may develop and persist in long Covid cases as shown by evidence in this study *[16,17]*.

According to the current study the increase in heart rate by about 40 bpmfrom supine to incline position in tilt table test with a statistically significant value (p<0.001). Postural orthostatic tachycardia syndrome was reported in an international online survey that involved 802 COVID-19 survivors *[18]*.

On the other hand, the change in systolic and diastolic blood pressurewas not statistically significantindicating no orthostatic hypotension.

Palpitation had a significant association with increased heart rate among the studied patients with a significant p-value of <0.0 as well asfatigue and dizziness after standingin line with Cui et al., who said that postural orthostatic tachycardia syndrome was accompanied by a series of discomforts such as fatigue, palpitations, dizziness, headache, chest tightness, and even syncope. However, no significant associations were observed between postural orthostatic tachycardia syndrome and other symptoms *[19]*.

Xie et al., showed that patients with severe COVID-19 requiring mechanical ventilation are 16 times more likely to develop ventricular tachycardia within six months compared to their peers without severe infection similar to our study. This is further confirmed as the patient with recorded tachycardia in our study was ventilated during her hospital stay and later developed tachycardia *[20]*.

Conclusion:

Children with history of COVID-19 infection have increased risk of autonomic dysfunction as orthostatic intolerance and/or postural orthostatic tachycardia syndrome. Tilt table test diagnosed postural orthostatic tachycardia syndrome in 20% of the studied patients. Patients with left ventricular dilatation have higher chance to develop elevated systolic blood pressure.

Postural orthostatic tachycardia syndrome was associated with palpitations as well as fatigue and dizziness after standing, dyspnea on exertion, headache. It was also associated with PICU admission.

Patients with a past positive PCR result were also significantly associated with postural orthostatic tachycardia syndrome compared to those with a negative result.

Further studies with larger sample size and longer follow-up are needed to confirm our results and to identify risk factors of adverse events.

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الخلل اللاإرادي لدى المرضى من الأطفال الذين يعانون من عدوى فيروس كورونا سابقة وتأثُر قلبي وعائي

المقدمة: تُظهر المراجعات والحالات المنهجية أن مرض فيروس كورونا المستجد، له علاقة بأعراض مختلفة بالجهاز العصبي اللاإرادي في مرضى سبق اصابتهم بالفيروس داخل المستشفى وخارجها.

الهدف من الدراسة: تستهدف هذه الدراسة تقييم وجود خلل وظيفي لا إرادي مثل انخفاض ضغط الدم الانتصابي وتسارع ضربات القلب الانتصابي الوضعي باستخدام اختبار الطاولة المائلة عن طريق دراسة قطعية قائمة على الملاحظة بوحدة القلب بمستشفى الأطفال بالدمرداش جامعة عين شمس في الفترة من ٢٠٢٣/٦/١ الى ٢٠٢٣/١١/٣٠.

المرضى وطرق العلاج: اعتمدت الدراسة على تحليل السجلات الطبية لـ ٢٥ حالة من تاريخ مرضي مفصل مع التركيز على فترة الاصابة ب كورونا ومضاعفاتها وفحص عام للمرضى وفحص موضعي لتقييم وجود أى مضاعفات خاصةً أعراض متلازمة الالتهاب متعدد الأجهزة والتركيز على اختبار الطاولة المائلة.

النتائج: أظهرت النتائج أن أغلب المرضى من الذكور معظمهم مصاب بمتلازمة الالتهاب المتعدد عند الأطفال ولديهم أعراض مستمرةمن بعد عدوى فيروس كورونا المتجدد. تم عمل اختبار الطاولة المائلة وكانت توجد نتيجة ايجابية بنسبة (٢٠,٠٪) و تأثير $p < ٠,٠٠١$

الخلاصة: الاطفال الذين سبق لهم الاصابة بفيروس كورونا أو مضاعتها و لديهم اعراض متبقية مثل احتمالية اقل للمجهود أو زيادة الوهن أو الصداع لديهم احتمالية اكثر بالاصابة بخلل وظيفي لاإرادى مثل تسارع ضربات القلب الانتصابي الوضعي و/أو انخفاض ضغط الدم الوضعي ويفضل عمل اختبار الطاولة المائلة.