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Original Article

The association of dynamic thiol-disulfide homeostasis and inflammatory markers in patients with polycystic ovary syndrome

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ABSTRACT

Objective: Polycystic ovary syndrome (PCOS) is a common hormonal disorder among women of reproductive age characterized by irregular menstruation and hirsutism and is associated with an increased risk for cardiovascular diseases. Increased inflammatory response and oxidative stress may also present in these patients. In this study, we aimed to compare the neutrophil-to-lymphocyte ratio (NLR), mean platelet volume (MPV), and dynamic thiol-disulphide homeostasis (dTDH) between the patients with PCOS and healthy individuals and to investigate the correlation between these parameters and cardiovascular risk factors in patients with PCOS.

Materials and methods: A total of 60 participants were included in this study. The patient group consisted of 36 patients who were diagnosed with PCOS and the control group consisted of 24 healthy individuals without PCOS. Complete blood count and hormonal tests were performed using blood samples. The NLR, MPV, and dTDH were compared between the patient and control groups.

Results: There was no statistically significant difference in the native thiol, total thiol, disulphide levels and disulfide/native, disulfide/total and native/total thiol ratios between the patient and control groups ($p = 0.494$, $p = 0.446$, $p = 0.338$, $p = 0.717$, $p = 0.723$, and $p = 0.717$, respectively). In addition, there was no statistically significant difference in NLR and MPV between the groups ($p = 0.531$ and $p = 0.196$).

Conclusion: Our study results showed no significant difference in the NLR, MPV, dTDH levels, and inflammatory biomarkers including leukocyte count between the PCOS patients and healthy controls. Based on these findings, we conclude that the diagnosis of PCOS alone in overweight patients has no considerable effect on these biomarkers.

Introduction

Polycystic ovary syndrome (PCOS) is a common hormonal disorder characterized by irregular menstruation, chronic anovulation, and clinic and/or biochemical hyperandrogenism with morphologically characteristic feature of polycystic ovaries. It mostly affects about 5–8% of women of reproductive age [1]. Although there are several well-known risk factors including impaired glucose tolerance, insulin resistance, type 2 diabetes mellitus, obesity, and hyperlipidemia, newly defined risk factors such as subclinical atherosclerosis and increased inflammatory response for cardiovascular diseases (CVD) have been shown in recent years [2,3].

High-sensitivity C-reactive protein (hsCRP) is used as an indicator of subclinical inflammation in patients with PCOS [4]. However, recent studies have demonstrated that increased leukocyte count is an independent biomarker and prognostic factor for inflammation and atherosclerosis [5–7]. In addition, neutrophil-to-lymphocyte ratio (NLR) has been shown to be a useful biomarker for inflammatory diseases such as PCOS and ulcerative colitis [5,8].

Platelets play a key role in the development of atherothrombosis [9]. Platelets with larger volume are more active metabolically and enzymatically with an increased prothrombotic potential [6]. The

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mean platelet volume (MPV) is a potential biomarker of platelet reactivation [10–12].

Reactive oxygen species (ROS) are reactive molecules which comprise both free and non-free radical oxygen intermediates involving in several physiological processes [13]. These radicals have a destructive effect on lipids, deoxyribonucleic acid (DNA), proteins, and cells and these deleterious effects can be prevented by the enzymatic and non-enzymatic antioxidant systems. In case of any impairment, oxidative stress occurs. Several studies have demonstrated that oxidative stress play a pivotal role in PCOS, infertility, insulin resistance, and increased CVD [14,15].

The thiol group, which is also known as mercaptans, contain a the sulfhydryl group (-SH), establishes a covalent bond with a disulphide bridge in case of oxidative stress. Disulphide bonds are re-reduced to thiol group to maintain the continuity of dynamic thiol-disulphide homeostasis (dTDH) [16]. The dTDH plays a central role in antioxidant defense mechanism, detoxification, and apoptosis [17].

In the present study, we aimed to compare the NLR, MPV, and dTDH between the patients with PCOS and healthy individuals and to investigate the correlation between these markers and CV risk factors in patients with PCOS.

Materials and method

This study was conducted at obstetrics and gynecology outpatient clinics of Bursa Yüksek İhtisas Training and Research Hospital between June 2018 and January 2019. Total of 60 participants were included in this study. The patient group consisted of 36 patients who were diagnosed with PCOS according to the Rotterdam criteria [18]. Diagnosis is dependent on the presence of at least two of the following three features: oligo/anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound. The control group consisted of 24 healthy individuals without any clinical, laboratory, and ultrasonographic evidence of PCOS. Exclusion criteria were as follows: having diabetes mellitus, hyperprolactinemia, Cushing syndrome, congenital adrenal hyperplasia, thyroid disorder, or hypertension; those receiving oral contraceptives, anti-androgens, acetylsalicylic acid, statin, or insulin-sensitizing agents within the past six months. A written informed consent was obtained from each participant. The study protocol was approved by the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital.(2011-KAEK-25 2019/04-20) The study was conducted in accordance with the principles of the Declaration of Helsinki.

The body weight, height, and body mass index (BMI) values were evaluated. The BMI values were calculated according to the following formula: weight (kg)/height (m^2). The waist circumference was measured using a tape measure narrowest part between the lowest rib and the iliac crest in the standing position, while the hip circumference was measured at the largest point at the level of the greater trochanters. Blood pressure were also measured.

Blood samples were collected after a 12-h overnight fasting between 08.00 and 10.00 AM on Days 2 and 5 of the menstrual cycle. Biochemical and hormonal analyses were performed. Complete blood count including MPV was analyzed using the Roche SYSMEX analyzer (Roche Diagnostics, Basel, Switzerland). In addition, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2), total testosterone, prolactin (PRL), dehydroepiandrosterone sulfate (DHEA-S), and insulin, 17-hydroxyprogesterone (17-OHP) were analyzed using the Abbott ARCHITECT® assay (Abbott Laboratories, Singapore). Fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) using the Beckman Coulter Synchron LX20 analyzer were also measured. Insulin resistance was calculated using the Homeostatic Model Assessment Insulin Resistance (HOMA-IR) formula (fasting glucose (mg/dL) x fasting insulin (μU/mL)/405). For the dTDH analysis, the sera were separated and kept at −80° until analysis. Thiol/disulphide homeostasis was determined using a novel spectrophotometric method developed by Erel and Neselioglu [17]. Reducible disulfide bonds were reduced to form free functional thiol groups. Unused reductant sodium borohydride was consumed and removed with formaldehyde, and all thiol groups including reduced and native thiol groups were determined after the reaction with 5,5′-dithiobis-(2-nitrobenzoic) acid (DTNB). Half of the difference between the total thiols and the native thiols was recorded as the dynamic disulfide amount. After the native thiols and total thiols were determined, disulfide amounts, disulfide/total thiol ratios, disulfide/native thiol ratios, and native thiol/total thiol ratios were calculated. Measurements were made using Cobas 501 automated clinical chemistry analyzer (Roche Diagnostics, Basel, Switzerland) and the results were given in μmol/L.

Statistical analysis

Statistical analysis was performed using the SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard deviation (SD), and number and frequency. The Shapiro-Wilk test was used to check the normality assumption. The Pearson chi-square test was used to compare the groups. The independent samples t-test and the Mann-Whitney U test were used to compare variables between the groups. A p value of <0.05 as considered statistically significant.

Results

A total of 60 participants were included in this study. The mean age was 26.86 ± 4.673 years in the patient group and 28.46 ± 4.539 in the control group. The smoking rate was 26% (n = 6) and 13.9% (n = 5) in the patient and control groups, respectively. There was no significant difference in the demographic characteristics between the patient and control groups. Baseline demographic and anthropometric characteristics of all participants are shown in Table 1.

Clinical and laboratory findings are presented in Table 2. The mean Ferriman-Gallawey Hirsutism scores, waist and hip circumferences, diastolic blood pressure, lymphocyte count, 17-OHP, DHEA-S, total testosterone, and LDL-C levels were significantly higher in the patients with PCOS than the control group (p = 0.001, p = 0.037, p = 0.049, p = 0.018, p = 0.018, p = 0.001, p = 0.005, p = 0.027, and p = 0.037, respectively). However, the PRL and FSH levels were higher in the control group (p = 0.027 and p = 0.001).

In addition, there was no statistically significant difference in the native thiol, total thiol, disulfide levels and disulfide/native, disulfide/total and native/total thiol ratios between the patient and control groups (p = 0.494, p = 0.446, p = 0.338, p = 0.717, p = 0.723, and p = 0.717, respectively). In addition, there was no statistically

Table 1
Demographic and anthropometric characteristics of patient and control groups.

	Control			PCOS			*P*
	N	Mean	SD	N	Mean	SD	
Age, year	24	28,46	4,539	36	26,86	4,673	0,051
Height, m	24	1,617	0,065	36	1,619	0,062	0,907
Weight, kg	24	67,00	16,00	36	74,21	16,98	0,105
BMI (kg/m^2)	24	25,51	5,39	36	28,19	5,63	0,071

N, number of patients; SD, standard deviation; PCOS, polycystic ovary syndrome.

Table 2
Clinical and laboratory findings of patient and control groups.

	Control			PCOS			N
	N	Mean	SD	N	Mean	SD	
Ferriman-Gallawey Hirsutism Score	24	10,08	7,47	36	17,58	8,33	0,001
Waist circumference, cm	24	83,63	12,75	36	90,81	12,82	0,037
Hip circumference, cm	24	103,92	10,34	36	109,92	11,78	0,049
SBP, mmHg	24	109,17	11,00	36	111,94	10,64	0,412
DBP, mmHg	24	64,79	10,37	36	71,50	9,02	0,018
TSH (μU/mL)	24	2,07	1,18	36	1,58	0,69	0,129
PRL (ng/mL)	24	20,36	9,27	36	15,29	8,47	0,027
FSH (mIU/mL)	24	6,17	1,61	35	4,66	1,39	0,001
LH (mIU/mL)	24	4,25	1,56	36	5,60	3,54	0,298
Estradiol (pg/mL)	24	47,31	26,59	36	35,97	12,34	0,160
Total testosterone, ng/dL	23	1,08	0,38	34	1,27	0,35	0,027
DHEA-S (μg/dL)	24	157,15	60,30	36	224,87	91,17	0,005
17-OHP (ng/mL)	23	0,50	0,61	35	1,29	0,97	0,001
Insulin (μU/mL)	24	11,77	15,90	36	11,45	6,65	0,086
Fasting blood glucose (mg/dL)	24	87,21	9,00	36	89,69	9,97	0,287
HDL-C (mg/dL)	24	52,75	13,33	36	48,53	11,27	0,160
LDL-C (mg/dL)	24	90,66	27,72	36	106,50	28,35	0,037
Total cholesterol (mg/dL)	24	169,83	31,14	36	177,06	32,92	0,399
TG (mg/dL)	24	101,25	75,76	36	101,44	42,40	0,287
CIMTORT (mm)	24	0,57	0,04	36	0,58	0,08	0,921
Native thiol (μmol/L)	24	334,78	46,81	36	344,74	59,56	0,494
Total thiol (μmol/L)	24	372,18	45,97	36	383,24	59,70	0,446
Disulfide (μmol/L)	24	18,70	4,57	36	19,25	4,07	0,338
Disulfide/native thiol (%)	24	5,74	1,98	36	5,76	1,63	0,717
Disulfide/total thiol (%)	24	5,10	1,49	36	5,13	1,28	0,723
Native/total thiol (%)	24	89,80	2,97	36	89,74	2,56	0,717
MPV (fL)	24	8,70	0,85	36	8,98	1,54	0,531
PLT (10^3/mL)	24	256,17	67,84	36	263,17	59,98	0,676
WBC (10^3/mL)	24	7,84	2,85	36	8,17	2,68	0,239
Neutrophil (10^3/mL)	24	5,09	2,77	36	5,00	2,45	0,483
Lymphocyte (10^3/mL)	24	1,99	0,68	36	2,47	0,84	0,018
NLR	24	3,08	3,02	36	2,30	1,57	0.196

N, number of patients; SD, standard deviation; PCOS, polycystic ovary syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; TSH, thyroid-stimulating hormone; PRL, prolactin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; DHEA-S, dehydroepiandrosterone sulfate; 17-OHP, 17-hydroxyprogesterone; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; MPV, mean platelet volume; NLR; neutrophil-to-lymphocyte ratio; PLT, platelet; and WBC, white blood count.

significant difference in NLR and MPV between the groups ($p = 0.531$ and $p = 0.196$).

The results of the correlation analysis are summarized in Table 3. There was a positive and significant correlation between the TG levels and disulfide, disulfide/native thiol ratio, disulfide/total thiol ratio, and platelet and lymphocyte counts ($p = 0.001$, $p = 0.001$, $p = 0.002$, $p = 0.000$, and $p = 0.003$, respectively). However, there was a negative and significant correlation between the native/total thiol ratio ($p = 0.002$). On the other hand, there was no significant correlation between the MPV values and clinical and laboratory parameters.

Table 4 shows the correlation of dTDH with the NLR, MPV, and leukocyte count. There was no significant correlation between the dTDH and the NLR, MPV, and leukocyte count.

Discussion

Platelets play a key role in the development of atherothrombosis [9]. Although several tools have been developed to evaluate the platelet activity in patients with an increased risk for CVD, their use is limited in clinical practice, as most of them are expensive and time-consuming and require an experienced team [19]. Mean platelet volume is also used for the measurement of the average size of platelets in blood and is a potential biomarker of platelet reactivation. Increased MPV has been shown to be associated with increased platelet aggregation, increased thromboxane synthesis, and increased expression of adhesion molecules [20].

In the literature, there are several studies suggesting an increased inflammatory response and subclinical atherosclerosis in patients with PCOS [2,3]. Some of these studies have utilized hsCRP, MPV, and NLR as the inflammatory indicators [4,5,8,11,12]. In a study, higher MPV values were reported in patients with PCOS than the healthy controls [21,22]. In another study, decreased in the MPV values were found after ethinylestradiol/cyproterone acetate or metformin treatment in PCOS patients, compared to the pre-treatment values [23]. In addition, Yilmaz et al. [24] showed higher NLR and MPV values in patients with PCOS than healthy controls, although the hsCRP levels were similar between the groups. When the patients were further divided into two subgroups according to the BMI as obese patients ($\geq$25 kg/m^2) and lean patients (<25 kg/m^2), MPV values were similar between the obese PCOS and control groups, while higher MPV values were observed in the lean PCOS patients compared to the control group. On the contrary, some other studies reported similar MPV values between the lean PCOS patients and healthy controls [25,26].

Furthermore, several studies have investigated whether elevated leukocyte count is an independent risk factor and prognostic indicator for inflammation and atherosclerosis [27]. Some authors found increased leukocyte count and NLR in patients with PCOS [5,24]. In our study, on the other hand, we found no significant difference in the NLR and MPV values between the overweight PCOS patients and healthy controls. In addition, we observed no significant difference in the insulin, fasting blood glucose, HDL-C, TG, and total cholesterol between the groups. These findings indicate no significant correlation between the NLR and MPV values and clinical and laboratory parameters.

Oxidative stress is caused by an imbalance between the production of ROS and antioxidant mechanisms. The ROS plays a

Table 3
Correlation analysis.

		Native thiol	Total thiol	Disulfide	disulfide/native thiol	disulfide/total thiol	native/total thiol	MPV	PLT	WBC	Neutrophil	Lymphocyte
SBP, mmHg	r	-,046	-,065	-,119	-,058	-,052	,052	,063	-,017	,118	,088	,129
	p	,727	,623	,364	,659	,693	,693	,633	,896	,370	,504	,327
DBP, mmHg	r	-,224	-,207	,114	,218	,219	-,219	,063	,051	,041	-,024	,225
	p	,086	,113	,384	,095	,093	,093	,635	,696	,756	,853	,084
TSH (μU/mL)	r	-,178	-,180	-,012	,072	,077	-,077	-,156	,212	,152	,117	,043
	p	,175	,169	,926	,586	,561	,559	,233	,104	,247	,373	,744
PRL (ng/mL)	r	,136	,134	-,013	-,105	-,098	,098	,195	-,038	-,166	-,184	,011
	p	,301	,307	,919	,424	,457	,456	,136	,776	,206	,159	,936
FSH (mIU/mL)	r	-,187	-,186	,009	,122	,121	-,121	,004	,031	-,145	-,077	-,243
	p	,157	,159	,947	,356	,362	,360	,975	,818	,274	,561	,063
LH (mIU/mL)	r	,202	,211	,054	-,041	-,039	,039	,087	-,055	-,149	-,149	-,007
	p	,122	,106	,684	,756	,770	,769	,511	,679	,255	,257	,957
Estradiol (pg/mL)	r	,033	,052	,117	,050	,055	-,054	-,112	-,101	-,308	-,293	-,108
	p	,800	,695	,374	,707	,677	,680	,393	,445	,017	,023	,411
Total testosterone, ng/dL	r	-,027	-,024	,018	,006	,016	-,015	-,167	,195	,008	-,083	,276
	p	,842	,859	,895	,966	,904	,909	,215	,146	,951	,540	,038
DHEA-S (μg/dL)	r	,112	,123	,070	-,047	-,035	,035	-,073	,051	,174	,127	,211
	p	,395	,350	,598	,722	,793	,789	,577	,696	,184	,332	,105
17-OHP (ng/mL)	r	-,118	-,114	,027	,088	,101	-,101	,071	,040	,047	-,029	,197
	p	,377	,393	,840	,511	,450	,451	,596	,766	,726	,829	,139
Insulin (μU/mL)	r	-,163	-,146	,108	,198	,194	-,195	-,137	,211	,324	,245	,213
	p	,214	,264	,412	,129	,136	,136	,295	,105	,011	,059	,102
Fasting blood glucose (mg/dL)	r	-,029	-,012	,114	,083	,075	-,074	-,167	,317	,099	,005	,279
	p	,823	,929	,386	,529	,570	,572	,203	,014	,453	,970	,031
HDL-C (mg/dL)	r	,219	,225	,034	-,091	-,088	,088	,208	-,360	-,235	-,100	-,426
	p	,093	,084	,797	,489	,506	,505	,111	,005	,071	,447	,001
LDL-C (mg/dL)	r	-,058	-,052	,043	,081	,081	-,081	-,095	,129	,323	,242	,279
	p	,657	,694	,745	,540	,538	,536	,468	,324	,012	,063	,031
Total cholesterol (mg/dL)	r	-,072	-,038	,216	,238	,236	-,236	-,063	,221	,273	,211	,222
	p	,586	,772	,098	,067	,070	,070	,635	,090	,035	,106	,088
TG (mg/dL)	r	-,061	,005	,423	,422	,400	-,400	-,154	,463	,213	,087	,382
	p	,644	,971	,001	,001	,002	,002	,241	,000	,103	,510	,003
CIMT	r	-,036	-,032	,024	,036	,032	-,032	-,154	-,079	-,135	-,130	-,058
	p	,787	,809	,853	,786	,808	,807	,240	,547	,302	,321	,661

SBP, systolic blood pressure; DBP, diastolic blood pressure; TSH, thyroid-stimulating hormone; PRL, prolactin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; DHEA-S, dehydroepiandrosterone sulfate; 17-OHP, 17-hydroxyprogesterone; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; MPV, mean platelet volume; NLR; neutrophil-to-lymphocyte ratio; PLT, platelet; and WBC, white blood count; CIMT, carotid intima media thickness.

Table 4
Correlation analysis of dTDH and inflammatory biomarkers.

		Native thiol	Total thiol	Disulfide	Disulfide/native thiol	Disulfide/total thiol	Native/total thiol
MPV (fl)	r	,131	,111	-,134	-,126	-,140	,140
	p	,318	,400	,307	,338	,285	,285
	n	60	60	60	60	60	60
PLT (10^3/ml)	r	-,178	-,127	,334	,364	,367	-,367
	p	,173	,335	,009	,004	,004	,004
	n	60	60	60	60	60	60
WBC(10^3/ml)	r	,043	,050	,045	,006	,006	-,005
	p	,744	,704	,734	,962	,966	,968
	n	60	60	60	60	60	60
Neutrophil (10^3/ml)	r	,079	,086	,039	-,021	-,020	,021
	p	,546	,515	,765	,876	,878	,876
	n	60	60	60	60	60	60
Lymphocyte (10^3/ml)	r	-,093	-,089	,027	,077	,074	-,074
	p	,478	,497	,837	,560	,575	,575
	n	60	60	60	60	60	60
NLR	r	,098	,097	-,007	-,070	-,067	,068
	p	,457	,461	,955	,597	,610	,608
	n	60	60	60	60	60	60

MPV, mean platelet volume; NLR; neutrophil-to-lymphocyte ratio; PLT, platelet; and WBC, white blood count.

pivotal role in the atherogenesis, resulting in oxidized LDL production, endothelial activation, and vascular smooth muscle cell proliferation [28]. It has been shown that PCOS and oxidative stress may induce cardiovascular complications [14,15,29].

In recent years, oxidative stress can be evaluated by a novel method developed by Erel and Neselioglu for the analysis of dTDH [17]. It has been suggested that dTDH plays a major role in the development of several conditions such as diabetes mellitus, PCOS, and coronary artery diseases [30,31]. In dTDH testing, disulfide, disulfide/native, and disulfide/total thiol ratios are the indicators of increased oxidative stress, while the native thiol and native/total thiol ratio are used as the antioxidant system indicators [17].

In their study including overweight and normal weight PCOS patients and a control group, Ozler et al. [28] found no statistically significant difference in the dTDH parameters between the groups. In addition, there was no statistically significant difference in the disulfide, disulfide/native, and disulfide/total thiol and native/total thiol ratios between the study and control groups. Similarly, we found no significant difference in the native thiol, total thiol, disulfide levels and disulfide/native, disulfide/total and native/total thiol ratios between the PCOS patients with a BMI of $\geq$25 kg/m^2 and healthy controls.

In another study investigating the association of oxidative stress with PCOS and abdominal obesity in serum and follicular fluid of infertile women, Nasiri et al. [32] reported that abdominal obesity could induce local and systemic oxidative stress in all patients with and without PCOS. Consistent with this finding, in our study, we also observed similar thiol results in both overweight PCOS patients and healthy controls. Similarly, Ozler et al. found no statistically significant difference in the disulfide, disulfide/native, disulfide/total thiol and native/total thiol ratios between the PCOS patients and healthy controls [28].

Review of the literature have also demonstrated a correlation between the oxidative stress and insulin resistance and total testosterone levels [33,34]. However, in the present study, we found no significant relationship between the thiol levels and clinical and laboratory parameters. On the other hand, we observed a positive and significant correlation between the disulfide, disulfide/native thiol ratio, and disulfide/total thiol ratio and platelet counts in patients with PCOS.

Nonetheless, there are some limitations to this study. First, the study has a relatively small sample size. Second, only overweight PCOS patients were included in this study and normal weight PCOS patients were unable to be evaluated. We, therefore, recommend further large-scale, long-term, prospective studies including patients with a wide range of BMI values to gain a better understanding of the relationship between PCOS and oxidative stress.

In conclusion, our study results showed no significant difference in the NLR, MPV, dTDH levels, and inflammatory biomarkers including leukocyte count between the PCOS patients and healthy controls. Based on these findings, we conclude that the diagnosis of PCOS alone in overweight patients has no considerable effect on these biomarkers. However, we believe that future studies of this topic would provide more robust evidence and increase our current level of understanding.

Funding

Not applicable.

Design

Cross-sectional study.

Setting

Bursa Yüksek İhtisas Training and Research Hospital, Bursa.

Ethical Disclosure

Protection of human and animal subjects: The authors declare that no experiments were performed in humans and animals for this investigation.

Confidentiality of Data

All authors of this manuscript declare that they have followed the protocols of publication of patient's data. All caregivers of the participants were informed in detail about the research and signed the patient informed consent.

Declaration of Competing Interest

All of the authors declare no conflicts of interest.

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