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Ischemia-modified albumin (IMA) and dynamic thiol-disulfide homeostasis in patients with postherpetic neuralgia

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Abstract

Background: Ischemia-modified albumin (IMA) is an isotype of albumin that increases under oxidative stress, and plasma thiols are main defense mechanisms against oxidative stress. The objective of this study was to investigate thiol-disulfide homeostasis and serum IMA levels in postherpetic neuralgia (PHN) patients.
Methods: A total of 29 PHN patients and 30 healthy controls were included in the study. Serum total and native thiol concentrations and serum disulfide concentration were measured using the method described by Erel and Neselioglu. The albumin cobalt binding test was used to measure serum IMA levels.
Results: Serum IMA levels were 1.21 ± 0.58 AU and 0.75 ± 0.09 AU in the PHN and control groups, respectively ($p < 0.001$). Serum total thiol concentrations were found to be 421.62 ± 90.28 μmol/L and 598.36 ± 73.63 μmol/L in the PHN and control groups, respectively ($p < 0.001$). Serum native thiol concentrations were found to be 365.75 ± 92.07 μmol/L and 531.90 ± 72.9 μmol/L in the PHN and control groups, respectively ($p < 0.001$). Serum disulfide concentrations were found to be 33.23 ± 5.33 μmol/L and 27.93 ± 7.81 μmol/L in the PHN and control groups, respectively ($p = 0.003$). The native thiol/total thiol ratio was significantly lower, and the disulfide/total thiol and disulfide/native thiol ratios were significantly higher in the PHN group compared to the controls.
Conclusions: IMA levels are high and dynamic thiol/disulfide homeostasis is disrupted in PHN patients.

Keywords: ischemia-modified albumin; oxidative stress; postherpetic neuralgia; thiol/disulfide.

Introduction

Herpes zoster (HZ) results from reactivation of the varicella zoster virus (VZV) which remains latent in the dorsal root ganglion following the initial infection. Reactivation of VZV is associated with decreased cell-mediated immunity [1]. Several factors including diabetes, cancer, surgery, organ transplantation, stress and negative life events have been stated as risk factors for HZ [2–6]. Psychological stress is a widely recognized risk factor and is thought to be a trigger for HZ [6].

Neuralgia along a dermatome and unilateral rash are typical clinical symptoms of HZ. Although rash usually improves within 2–4 weeks, HZ complications may develop. The most common complication of HZ is postherpetic neuralgia (PHN), which is generally defined as pain lasting longer than 90 days after improvement of rash [7, 8]. Several risk factors for the development of PHN in HZ patients have been reported including age, gender, clinical features of HZ episode, chronic morbidity, immunosuppression and cancer [9].

Thiols are organic sulfur derivatives containing sulfhydryl residues (–SH) in their active regions. Thiols easily react with oxygen-containing free radicals to form disulfides. This is a defense mechanism against oxidative stress. Disulfide bonds can be reduced back to thiol groups, thus thiol/disulfide homeostasis is preserved [10]. An automated analysis quantitatively measuring serum native and total thiol, and disulfides has been recently described as a method to determine dynamic thiol/

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disulfide homeostasis [11]. It is easy to perform this new test in routine clinical laboratories, and it is a sensitive method to observe the oxidative stress status of the body.

Oxidative stress also affects the structure of the albumin, which is the most abundant protein in the plasma. The N-terminal region of albumin contains a binding location for transitional metal ions including cobalt and copper [12]. Ischemia and oxidative stress modify this terminal peptide region to an irreversible dysfunctional form known as ischemia-modified albumin (IMA). The level of IMA is associated with the degree of oxidative stress and also with the severity of the underlying disease [13, 14].

The objective of this study was to investigate serum IMA levels and dynamic thiol/disulfide homeostasis in PHN patients in order to determine whether oxidative stress, which plays an important role in the development of many diseases, is involved in the development of PHN, which occurs as a complication in HZ.

Materials and methods

Selection of participants

A total of 29 patients admitted to a pain outpatient clinic and diagnosed with PHN between 2017 and 2018, and 30 age-matched control subjects at the same period of time were included in the study. Patients receiving any antiviral treatment in another hospital before the visit to our hospital, those receiving any anti-inflammatory analgesic drugs for pain control before the treatment and patients with irregular follow-up were excluded from the study. The control group consisted of healthy people without HZ who were not immunized for HZ within the last year and having no family or autoimmune disease history and who had similar age and gender distribution.

This study was approved by the local Ethics Committee of our hospital (ethics no: 2018/1500). Informed consent forms were received from all patients. Demographic data (age, gender), educational status and comorbidity status of the patients with PHN were questioned and recorded. Patients were also questioned about whether they were immunized for VZV after the diagnosis of HZ and how long after HZ they developed PHN. Pain intensity of the patients at admission was evaluated using the visual analogue scale (VAS). In addition, dermatomes with the pain localized were recorded. Blood samples were collected from the patients in order to evaluate disulfide/thiol homeostasis and IMA levels. Treatment plans of the patients were arranged by an algologist who was not included in the study. Medical and interventional treatment methods applied were recorded from the patient files.

Plasma sampling, analytical procedure and laboratory methods

Venous blood samples were collected through antecubital vein from the voluntary patient and control groups. Blood samples were centrifuged at 3500 rpm for 10 min at 4 °C within 30 min after the sample collection from the participants. Serum obtained was kept frozen at −80 °C. Serum disulfide/thiol homeostasis measurements were made using the spectrophotometric method described by Erel and Neselioglu [11]. First, reducible disulfide bonds were reduced in order to form functional thiol groups. After reaction with 5,50-dithiobis-(2-nitrobenzoic acid) (DTNB), reducer sodium borohydride in the medium was depleted and removed using formaldehyde, and thus all thiol groups including reduced and native thiol groups were determined. Half of the difference between total thiol and native thiol was calculated as the disulfide level. After measuring native thiols (SH) and total thiols (SH + SS) and the amount of disulfides (SS), disulfide/total thiol ratio (index 1), disulfide/native thiol ratio (index 2) and native thiol/total thiol ratio (index 3) were calculated.

The albumin cobalt binding test was used to measure serum IMA levels.

This test was carried out by addition of 50 mL 0.1% cobalt (II) chloride ($CoCl_2$, $6H_2O$) (Sigma-Aldrich Chemie GmbH, Steinheim, Germany) to the patient serum. After centrifugation, serum samples were incubated for 10 min to allow binding of albumin to cobalt, and then 50 mL 1.5 mg/mL dithiothreitol (DDT) was added. After centrifugation and incubation for 2 min, 1.0 mL 0.9% sodium chloride solution was added to the milieu. Absorbance of the samples was read at 470 nm using a spectrophotometer, and the results were expressed in absorbance units (AU) [15]. Serum IMA/albumin ratio (IMAR) was also calculated.

Statistical analysis

Results of this study were analyzed using SPSS 19.0 software (IBM Corp., Armonk, NY, USA). Continuous values were expressed as mean ± standard deviation (SD) and categorical values as number and percentage (n, %). Normal distribution of the data was analyzed using the Kolmogorov-Smirnov test, histogram and ±SD. Non-parametric data of the groups were compared using the

Mann-Whitney U test and parametric data using the independent T test. Comparison of the categorical data was done using the chi-square test. Receiver operating characteristic (ROC) analyses were performed to test the ability of serum albumin, native thiol, total thiol, disulfide, index 1, index 2, index 3, IMA and IMAR to differentiate PHN patients from healthy controls. Optimal cut-off values were determined for each parameter, and sensitivity, specificity, positive predictive and negative predictive values were calculated. Linear regression analysis was used to determine independent predictors of thiol/disulfide parameters. Correlations between thiol-disulfide homeostasis parameters, albumin and IMA were evaluated using Spearman's correlation analysis. $p < 0.05$ values were considered statistically significant.

Results

Demographic and clinical features of patients

A total of 29 PHN patients and 30 control subjects were included in the study. The mean age was 56.89 ± 15.19 years in the PHN group (Group PHN) and 56.20 ± 13.20 years in the control group (Group C) ($p = 0.851$). The female/male ratio was 21/8 (72.4%/27.6%) in Group PHN and 21/9 (70%/30%) in Group C ($p = 0.838$). Of the PHN patients, 26 (89.7%) were literate and three (10.3%) were illiterate. Five (17.24%) patients had accompanying malignancies. There were no other comorbidities in the PHN group except the aforementioned malignancies. While 25 patients in the control group were literate (83.3%), five patients (16.7%) were illiterate. There was no comorbidity in the control group. Considering the pain intensity on admission, the mean VAS score was 7.5 ± 0.91 (min–max: 6–10) in the PHN group. None of the patients were vaccinated for VZV. Time to PHN development following HZ was 3.6 ± 1.03 months (min–max: 3–6). Thoracal dermatoma was involved in 25 (86.20%) patients. Interventional treatment modalities were performed in 13 (44.82%) patients in addition to medical therapy.

Laboratory outcomes of patients

Serum IMA levels were 21 ± 0.58 AU and 0.75 ± 0.09 AU in the PHN and control groups, respectively, and the difference between the groups was statistically significant ($p < 0.001$). Serum total thiol concentrations were 421.62 ± 90.28 μmol/L and 598.36 ± 73.63 μmol/L in the PHN and control groups, respectively ($p < 0.001$). Serum native thiol concentrations were 365.75 ± 92.07 μmol/L and 531.90 ± 72.9 μmol/L in the PHN and control groups, respectively ($p < 0.001$). Serum disulfide concentrations were 33.23 ± 5.33 μmol/L and 27.93 ± 7.81 μmol/L in the PHN and control groups, respectively ($p = 0.003$). The native thiol/total thiol ratio was significantly lower, and the disulfide/total thiol and disulfide/native thiol ratios were significantly higher in the PHN group compared to the controls (Table 1, Figure 1).

ROC analyses

ROC analyses were performed to test the ability of dynamic thiol/disulfide parameters, IMA and IMAR to distinguish

Table 1: Comparison of total thiol-disulfide hemostasis parameters, albumin and IMA levels of the postherpetic neuralgia and control groups.

	Group PHN (n = 29)	Group C (n = 30)	95% CI lower/upper	p-Value
Age, years	56.89 ± 15.19	56.20 ± 13.20	−8.11/6.71	0.851
Gender, F/M	21/8 (72.4%/27.6%)	21/9 (70%/30%)		0.838
Albumin, mg/dL	3.95 ± 0.57	5.33 ± 0.49	1.09/1.65	<0.001
IMA, AU	1.21 ± 0.58	0.75 ± 0.09	−0.68/−0.24	<0.001
IMAR (IMA/albumin), %	0.31 ± 0.18	0.14 ± 0.02	−0.240/−0.106	<0.001
Native thiol, μmol/L	365.75 ± 92.07	531.90 ± 72.9	122.93/209.37	<0.001
Total thiol, μmol/L	421.62 ± 90.28	598.36 ± 73.63	133.86/219.62	<0.001
Disulfide, μmol/L	33.23 ± 5.33	27.93 ± 7.81	1.81/8.77	0.003
Disulfide/total thiol, %	8.29 ± 3.61	6.38 ± 1.52	−3.34/−0.47	0.01
Disulfide/native thiol, %	6.95 ± 2.58	5.62 ± 1.17	−2.36/−0.28	0.013
Native thiol/total thiol, %	86.07 ± 5.04	88.74 ± 2.34	0.59/4.73	0.013

IMA, ischemia-modified albumin; AU, absorbance units; IMAR, ischemia-modified albumin/albumin ratio.

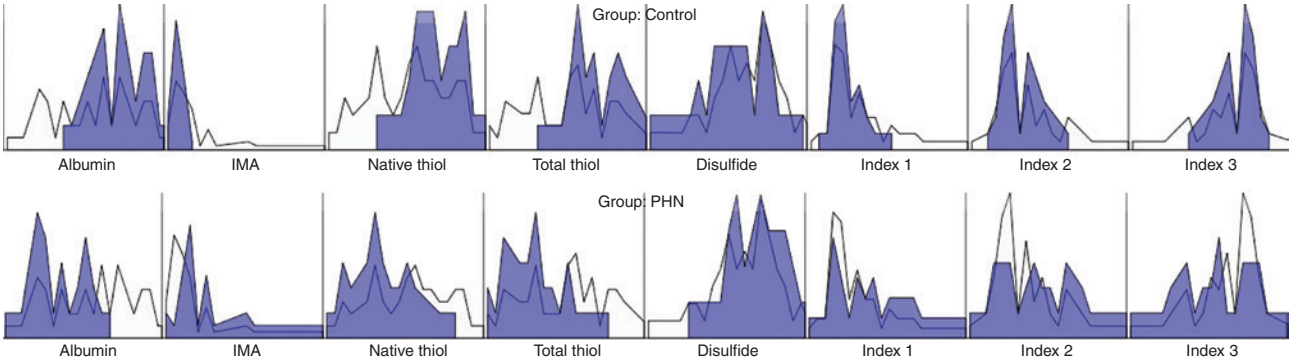

Figure 1: Serum thiol-disulfide homeostasis parameters, albumin and IMA levels of the groups.
IMA, ischemia-modified albumin; Index 1, disulfide/total thiol; Index 2, disulfide/native thiol; Index 3, native thiol/total thiol.

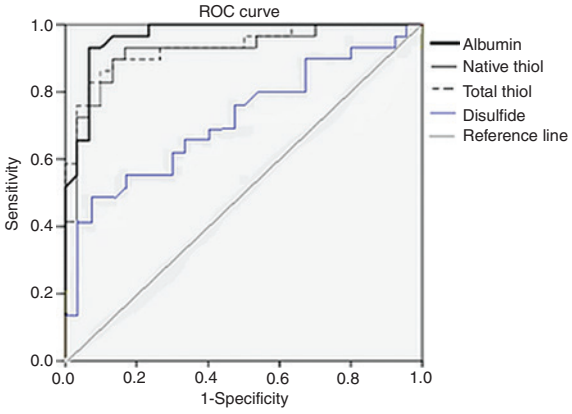

Figure 2: ROC curves for serum albumin, native thiol, total thiol and disulfide concentrations to differentiate postherpetic neuralgia patients from the healthy control group.

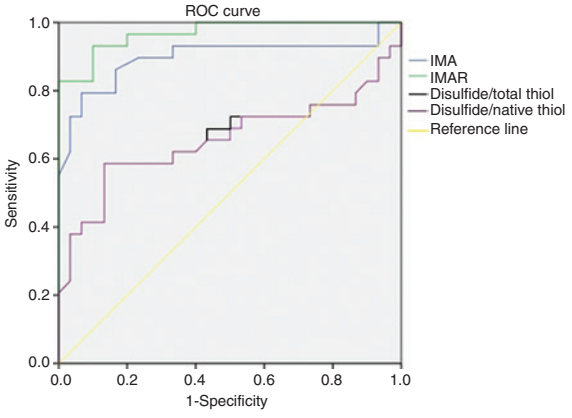

Figure 3: ROC curves for serum IMA, IMAR, disulfide/total thiol and disulfide/native thiol concentrations to differentiate postherpetic neuralgia patients from the healthy control group.

patients with PHN from healthy controls. ROC curves are given in Figures 2 and 3, and the results of the ROC analyses are summarized in Table 2.

Regression/correlation analysis

In the linear regression analysis, age was found to be an independent factor in the prediction of serum albumin (B: −0.022; β: −0.582; 95% confidence interval [CI]: −0.044/−0.001; p = 0.044), index 1 (B: 0.165; β: 0.692; 95% CI: 0.027/0.302; p = 0.022), index 2 (B: 0.115; β: 0.047; 95% CI: 0.017/0.213; p = 0.024) and index 3 (B: −0.228; β: −0.672; 95% CI: −0.423/−0.032; p = 0.025). On the other hand, the presence of malignancy was not an independent risk factor for elevated oxidative parameters.

There were significant correlations between thiol-disulfide homeostasis parameters, IMA and serum albumin levels (Table 3).

Discussion

PHN is an important complication of HZ infection. Although there are several well-defined risk factors such as age, immunosuppression and cancer, the exact pathogenesis of HZ reactivation and PHN is still unknown. The results of our study show that serum total and native thiol concentrations were decreased and serum disulfide concentration was increased in PHN patients. Thiols have a negative standard reducing potential. Therefore, they function as rapid electron recipients. When an oxidant interacts with a thiol group, the thiol is oxidized to form a disulfide at the same time neutralizing the oxidant substance to relatively less toxic by-products. Plasma levels of total thiol, native thiol and disulfide are increasingly investigated in the clinical diagnosis and follow-up of numerous diseases and metabolic disorders [16, 17]. Our finding indicates the shifting of dynamic thiol/disulfide homeostasis toward the disulfide side which implies the presence of oxidative stress in PHN patients.

Table 2: ROC analyses.

	AUC	p-Value	95% CI	Sensitivity	1-specificity	+Predictive	–Predictive	Cut-off
Albumin	0.966	<0.001	0.924–1000	93.1	93.3	93.1	93.3	4.80
IMA	0.897	<0.001	0.804–0.989	86.2	83.3	83.3	86.2	0.822
IMAR (IMA/albumin)	0.969	<0.001	0.932–1000	93.1	90	90	93.1	0.17
Native thiol	0.923	<0.001	0.852–0.994	89.7	86.7	86.7	89.6	462.5
Total thiol	0.933	<0.001	0.870–0.997	86.2	90	89.2	87.1	518.25
Disulfide	0.717	0.004	0.584–0.850	55.2	83.3	76.2	65.8	28.02
Disulfide/total thiol	0.659	0.036	0.510–0.809	58.6	86.7	80.9	68.4	7.475
Disulfide/native thiol	0.656	0.040	0.506–0.805	58.6	86.7	80.9	68.4	6.505
Native thiol/total thiol	0.657	0.038	0.508–0.807	62.1	66.7	64.3	64.4	88.06

IMA, ischemia-modified albumin; IMAR, ischemia-modified albumin/albumin ratio; AUC, area under curve; CI, confidence interval.

Table 3: Correlations between thiol-disulfide homeostasis parameters, albumin and IMA.

	IMA	IMAR	Native thiol	Total thiol	Disulfide	Disulfide/ total thiol	Disulfide/ native thiol	Native thiol/ total thiol
Albumin	ρ: −0.401[b] p = 0.002	ρ: −0.607[b] p < 0.001	ρ: 0.749[b] p < 0.001	ρ: 0.749[b] p < 0.001	ρ: 0.200 p = 0.129	ρ: −0.450[b] p < 0.001	ρ: −0.450[b] p < 0.001	ρ: −0.452[b] p < 0.001
IMA		ρ: 0.933[b] p < 0.001	ρ: −0.210 p = 0.110	ρ: −0.248 p = 0.059	ρ: −0.365[b] p = 0.004	ρ: 0.019 p = 0.885	ρ: −0.044 p = 0.736	ρ: 0.045 p = 0.736
IMAR			ρ: −0.348[b] p = 0.007	ρ: 0.378[b] p = 0.003	ρ: −0.340[b] p = 0.008	ρ: 0.085 p = 0.520	ρ: 0.067 p = 0.615	ρ: 0.067 p = 0.614
Native thiol				ρ: 0.993[b] p < 0.001	ρ: 0.184 p = 0.164	ρ: −0.697[b] p < 0.001	ρ: −0.691[b] p < 0.001	ρ: 0.692[b] p < 0.001
Total thiol					ρ: 0.297[a] p = 0.023	ρ: −0.617[b] p < 0.001	ρ: −0.607[b] p < 0.001	ρ: 0.608 p < 0.001
Disulfide						ρ: 0.511[b] p < 0.001	ρ: 0.541[b] p < 0.001	ρ: −0.540[b] p < 0.001
Disulfide/total thiol							ρ: 0.997[b] p < 0.001	ρ: −0.997[b] p < 0.001
Disulfide/native thiol								ρ: −1.000 p < 0.001

IMA, ischemia-modified albumin; IMAR, ischemia-modified albumin/albumin ratio; ρ, Spearman's rho correlation coefficient. [a]p < 0.05; [b]p < 0.001.

Our results also show that serum IMA levels were increased in PHN patients. IMA is a marker of ischemia and also an indicator of oxidative stress. The metal-binding capacity of albumin N-terminal decreases in acute ischemic conditions, and a variant protein known as IMA is formed [18]. Hypoxia/ischemia induces IMA by separation of the first two amino acids (Asp-Ala) of the N-terminal of the albumin which is a potent binding region for transitional metal ions [19, 20]. IMA production is induced by direct stimulation of oxidative stress and serum IMA levels may immediately increase within an hour [20]. Serum IMA levels were shown to increase in several diseases associated with oxidative stress [21].

The results of the current study show that oxidative stress is present in PHN patients. Both the increase in serum IMA levels and the shift of dynamic thiol/disulfide homeostasis toward the disulfide side are consistent with the presence of oxidative stress. Therefore, our results implicate that oxidative stress may contribute to the pathogenesis of PHN. There are only a few studies investigating the possible role of oxidative stress in HZ and PHN patients. Recently, Khazan et al. found that total antioxidant capacity and total polyphenol content levels were decreased and serum total oxidant status and oxidative stress index were increased in HZ patients [22]. In a meta-analysis conducted by Sebastiano et al., it was found that oxidative stress is increased across multiple tissues and species in vertebrates including mammals and humans. They also found that administration of antioxidants reduces virus yield, indicating that a condition of oxidative stress is favorable for the viral replication [23]. To the best of our knowledge, this is the first study

in the literature to investigate dynamic thiol/disulfide homeostasis in PHN patients using the method of Erel and Neselioglu [11].

HZ occurs with the reactivation and replication of latent VZV in sensory ganglion obtained during primary infection [24]. It is characterized by a vesicular rash confined to a single dermatome. The pathogenesis underlying the reactivation of VZV is unclear. However, any factor affecting cell-mediated immunity may play a role in the reactivation of VZV. There is consensus on that T-cell immunity plays a key role in the control of the reactivation. The causes of HZ have been poorly defined [7, 9, 25]. Age, stress, immunodeficiency and immunosuppressive drugs are the known risk factors for virus reactivation [26]. Previous clinical and experimental studies have associated mental stress and related psychosocial factors with the risk for HZ as well as cell-mediated immunity [8, 27]. Exposing stress or corticostress during infection with VZV increases the risk of HZ development by suppressing CD8+ T cellular immune response [27–29]. HZ develops 3.6 times higher in persons with a lower VZV-specific cell-mediated immunity (skin test with varicella antigen Biken <5 mm) than in individuals with a higher immunity (skin test with varicella antigen Biken ≥5 mm [30, 31].

Although HZ rash improves in a few weeks, HZ complications may be seen. PHN, which is defined as dermatomal pain persisting at least 3 months after the onset of HZ rash, is the most common complication [7]. The incidence of PHN is high following HZ. PHN1 has been reported in 19.5% of patients with HZ (pain persisting at least 1 month after rash onset), and PHN3 in 13.7% of patients with HZ (pain persisting at least 3 months after rash onset) [32].

Age is the most prominent and widely accepted risk factor for PHN, but the role of sex is controversial. Understanding the role of age and gender in PHN is important, because these are primary vaccine-targeted (namely this can be defined before HZ episodes) patient characteristics. Some studies found no association with sex [9], while others have reported that women are more likely to develop PHN and a similar increase in possibility is seen by increasing age [33]. Independent of age, underlying diseases such as diabetes, congestive heart failure (CHF) or chronic obstructive pulmonary disease (COPD) and malignancy seem to increase the risk and severity of PHN [34–36]. In our study, the mean age of PHN patients was 56.89±15.19 years (min–max: 25–88), and the incidence of PHN was higher in female than in male patients. In the regression analysis, age was an independent risk factor in the prediction of the levels of albumin, indices 1, 2 and 3, while malignancy was not evaluated as an independent risk factor for the elevation of oxidative parameters.

In this study, sensitivity and specificity values calculated for IMA, IMAR, native thiol and total thiol in order to distinguish PHN patients from the healthy controls were high.

Our results show that changes in serum native thiol/total thiol ratio, disulfide/total thiol ratio and disulfide/native thiol ratio were significant. In addition to individual measurements of serum native thiol, total thiol or disulfide concentration, determination of all parameters of dynamic thiol/disulfide homeostasis using Erel and Neselioglu's method may be appropriate in PHN patients.

One of the limitations of the current study was the fact that healthy controls were selected on the basis of medical history and detailed physical examination. Detailed laboratory tests were not performed in the control group.

In conclusion, disulfide/thiol homeostasis of PHN patients is disrupted, and shifts toward the disulfide side, which supports oxidative stress in the pathogenesis of the disease. Further studies are needed in order to clarify pathophysiological mechanisms underlying this disease. A better understanding of these mechanisms will facilitate development of new strategies in the prevention of PHN.

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