Effect of serum bisphenol A and low T3 on short-term prognosis of young patients with intracerebral hemorrhage

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Research Article

Keywords: Bisphenol A, Young patient, Intracerebral hemorrhage, Low T3 syndrome, Sub-clinical hypothyroidism, miRNA-451/miRNA338-3p, Biomarker

Posted Date: November 8th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1058244/v1>

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Abstract

Background

Bisphenol A (BPA) is widely present in daily necessities, and its exposure is almost everywhere. We aimed to evaluate the relationship between serum BPA levels, biomarkers and recent mortality in young patients with intracerebral hemorrhage (YICH) and low T3 .

Methods

Using a multi-center longitudinal prospective study, the research team recruited 600 YICH patients and divided into two subgroups according to their thyroid function, of which 320 (53.3%) were in the LT3, Sub-clinical hypothyroidism (SCH) was 280 (46.6%) and control group (n = 600).All patients received serum BPA, and biomarker blood draws.

Results

Calculating the cumulative quantification of plastic bag products, BPA increased by 0.204 standard deviation unit per log unit ($P<0.003$). Serum BPA, thrombin and matrix metalloproteinase (MMP-9) {BPA (0.91 ± 0.14) vs (0.765 ± 0.13) vs. (0.535 ± 0.11) pg/ml, thrombin (1.35 ± 0.18) vs (0.66 ± 0.15) vs (0.66 ± 0.15) ng/ml, MMP-9 (104 ± 10 vs (53 ± 8.1) vs (53 ± 8.1) pg/ml, both $P<0.01$ }. Linear correlation analysis showed that serum BPA was positively correlated with miR-388-3p and 24hDBPCV, and negatively correlated with LT3 and miR-451. Multiple linear regression showed that BPA affected the increase of nDBP Percentage of independent risk factors ($\beta = 0.286$), $P < 0.01$. Mortality rate showed 2 ,15 and 30 days of patients in the LT3 and the SCH of 4.7%vs 2.5%,6.25% vs 3.75%,4.68%vs 2.5%, $P<0.01$.

Conclusion

High BPA exposure strongly predicts the risk of ICH in young patients. The activation of NF- κ B signaling pathway, secondary thyroid function, ambulatory blood pressure scores, and changes in messenger ribonucleic acid construct an inflammatory response system. There are also significant differences in recent mortality between the LT3 group and the SCH group.

Trial registration

The trial is registered at clinical .gov (www.medresman.Chi CTR1900023626)

Highlights

1. Our study proved for the first time that serum BPA levels in young patients with intracerebral hemorrhage (YICH) are significantly increased, which may be a key and new finding.
2. There are obvious gender differences in serum bisphenol A levels in YICH patients, and this difference is related to the significant decrease in serum testosterone levels of functional hormones caused by the body's stress response.
3. It reveals the obvious inflammatory response after cerebral hemorrhage, the activation of cytokines, and the formation of a complete inflammatory network system, from biological agents to cytotoxicity and gene toxicity. Shows the difference in the temporal expression of biomarkers .
4. In BPA-related YICH patients, there are changes in ambulatory blood pressure (especially nocturnal diastolic blood pressure, blood pressure score), gender differences in thyroid function stress changes, and the combined effect of long-term accumulation of BPA.
5. In patients with IYICH, there is a significant difference in the recent mortality between the low T3 group and the sub-clinical hypothyroidism group.

Introduction

Intracerebral hemorrhage (ICH) accounts for 10–15% of stroke cases, and the assessment of risk factors for ICH is clinically challenging^[1,2]. Common mutations in gene locus, vascular risk factors (hypertension or blood pressure variability), peripheral gene toxicity and dynamic changes of immune cells are closely related to the risk of stroke^[3,4]. For this reason, exploring the unique field of interaction between self-protective neuroimmune inflammation and messenger ribonucleic acid will likely bring strategic positioning to the long-term prognosis or treatment of ICH^[5]. This study focuses on the changes in the levels of bio-trigger BPA gene toxicity and neurotoxicity and inflammation markers, in order to further evaluate the relationship between multiple proteases targeted in ICH and BPA, which will help patients with cerebral hemorrhage Neurotoxic molecular research provides in-depth new insights.

BPA is an industrial chemical that exists widely in the environment. Humans are exposed to BPA through food, milk, and skin contact^[6,7]. High levels of BPA exposure are related to abnormal regulation of thyroid ,autoimmune functions, obesity and metabolism^[8,9]. However, at current exposure levels in developing world the link between ICH and BPA remain unproven.This study focuses on clarifying the relationship between the cumulative quantification of BPA exposure levels and the risk of ICH, and assessing the correlation between different thyroid function,ambulatory blood pressure (ABP),miRNA,biomarkers and recent mortality.

Material And Methods

Patient

Analyze the clinical data of 600 YICH patients admitted to the Department of Intensive Care and Neurology, Changzhi People's Hospital. Changzhi Medical College Peace Hospital and Changzhi Second People's Hospital from January 2011 to January 2014. All selected cases are used Systematic sampling, multi-center and randomized controlled studies. According to the level of thyroid function, they were divided into two subgroups, including 320 (53.3%) in the LT3 and 280 (46.6%) in the SCH. Meets the criteria of the American Stroke Association, Clinical Neurology Committee^[10]. Exclusion criteria: (1) Liver and kidney damage, visceral malignant tumors, history of diabetes, family history of hypertension and previous use of aspirin. (2) Patients with cerebrovascular malformations and cerebrovascular tumors found in computed tomography must be excluded through cerebrovascular angiography.

The normal control group is selected strictly according to the screening criteria: a history of long-term exposure to plastic products are not eligible, healthy individuals (n = 600) matching age and gender.

Follow-up data

The methods include household entry, community visits, telephone calls, and reporting. Investigation of long-term exposure to plastic products: understand the use of plastic bottles from the time of infancy, children, adolescents, and adults who have habitually contacted or used plastic bags, especially the fried dough sticks were taken out of the oil pan and put into the plastic bag for breakfast. The establishment of product quantitative. Additionally, collect routine life data, including patient medication history, smoking and drinking history, body mass index (BMI): BMI = weight (kg) / height² (m²). Smoking is defined as continuous cumulative smoking for 6 months or more; drinking is defined as drinking at least one glass of wine in the past 30 days.

24h ABP monitoring

Strictly follow the 24-hour ABP inspection precautions and standards, and use the following measurement parameters: 24hSBP, 24hDBP, dSBP, dDBP, nSBP, nDBP; BP variability and coefficient of variation (BPV, CV), 24h SBPCV, 24hDBPCV; dSBPCV, dDBPCV; nSBPCV, nDBPCV; The coefficient is equal to the standard deviation / average BP. The diagnostic criteria for hypertension are SBP ≥ 140 and DBP ≥ 90 mmHg (1 mmHg = 0.133 kpa)^[11].

Serum analysis

Serum samples were collected on an empty stomach in the morning on the 2, 15 and 30 days after admission. The enzyme-linked immunosorbent assay measures BPA, thrombin, and MMP-9 from Shenzhen Galvanomi Biotechnology Co., Ltd. Provided; Electrochemiluminescence immunoassay measurement of total testosterone and free testosterone are provided by Bayer; triiodothyroxine (T3) and free triiodothyroxine (FT3), thyroxine (T4), free thyroxine (FT4) and Thyroid Stimulating Hormone (TSH) provided by Shanghai Science Co., Ltd.

TLR4-NF-κB signaling pathway related protein expression:

Collect peripheral venous blood, separate mononuclear cells, use Western Blot method to detect, Toll-like receptor 4 (TLR-4), Myeloid differentiation factor 88 (My88), (TRAF6) tumor necrosis factor-associated factor 6, nuclear transcription factor κBp65 (NF-κBp65). The protein was extracted from mononuclear cells with RIPA lysis buffer containing protease inhibitors, and the color was developed using a chemiluminescence kit. Perform quantitative analysis on the image and calculate the relative expression of each protein.

Expression of miRNA338-3p and miRNA144/451 in peripheral blood lymphocytes

Take 2ml of fasting venous blood was drawn from the survey subjects, and total RNA was extracted by the Trizol method. Real-time fluorescence quantitative polymerase chain reaction (PCR) method to detect the expression level of miRNA: using total RNA as a template, using random primers for reverse transcription amplification synthesis, obtaining miR-338-3p, miR144/451 internal reference Gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) RNA cDNA template; specific PCR primers were used to detect the expression of miRNA and GAPDH genes, and the 2^{-ΔΔCt} method was used to analyze the expression of indicators.

Statistical analysis

General demographic data is the mean ± SD of continuous variables and the percentage of categorical variables. The qualitative data comparison adopts one-way analysis of variance and chi-square test, and the main statistical indicators are tested for normality. First, the Mann-Whitney U test is used to assess the average difference between the two groups. The comparison of the means of the two large samples of the group design uses the U test. The comparison of the three sets of data uses F test. The changes of serum BPA concentration, cytokines, protease and 24hBP were analyzed by linear correlation analysis, regression analysis was used to determine the correlation between BPA concentration and thyroid function; through multiple linear regression analysis, the influence of various factors on the percentage of nSBP and nDBP was analyzed. Use receiver operating characteristic curve (receiver operating characteristic curve, ROC curve) to define the boundary value of miRNA high and low expression level; use cross-sectional analysis combined with Logistic regression model to analyze the combination of serum BPA, ABP and miRNA expression levels, cross-effects, and calculate relative Risk ratio attribution ratio and interaction index. Using SPSS v20.0 software (SPSS Inc, USA) for statistical analysis, the difference was statistically significant, P < 0.05.

Results

There were 240 males and 80 females in the LT3 group (75% vs 25%); 80 males and 200 females in the SCH group (28,57% vs 71.42%); the average age was 25 ± 7.2 years, and the control group was 25.3 ± 6.6 years old. Compared with the control group, 24hSBP, 24hDBP, insulin resistance-index, blood lipids, etc. increased in all YICH patients, especially nDBP increased significantly, $P < 0.05$. Additionally, calculating the cumulative amount of plastic bags for 10 years, each bag is 1.6 grams, 3000 bags, the total is about 4800g. For every log unit increase in BPA, it is determined that the Z score of the plastic bag increases by 0.204 standard deviation units ($P < 0.003$). (Table 1)

Table 1
Characteristics of the population

variable	LT3 (n = 320)	SCH (n = 280)	Control(n = 300)	P value
Mean age, (range)	25.4± 4.88	25.5± 6.29	25± 7.285	0.39
Male, n (%)	280 (87.5)**	80 (28.57)	300 (50)	0.05
Married n (%)	218 (68.1)	165(58.9)	300(62.5)	0.20
BMI (kg/m2)	23.7±4.1*	23 ± 5.1*	21.1 ± 3.3	0.05
FPG (mmol/L)	5.8 ± 1.24**	5.2 ± 0.9*	4.8 ± 0.8	0.05
HOMA-IR, (g/L)	3.5 ± 1.2**	3.2 ±1.3*	2.6 ±1.2	0.05
24hDBP (mmHg)	86.± 18.8**	82 ±9.1*	69 ±6.3	0.01
nDBP (mmHg)	86 ± 15**	82±11*	70 ±14	0.01
TG (mmol/L)	1.61 ± 0.8*	1.4 ± 0.9	1.27 ± 0.9	0.05
Tch (mmol/L)	5.23 ± 1.9**	4.8 ± 1.4*	3.8 ± 1.4	0.01
HDL-C (mmol/L)	0.98± 0.09*	1.1 ± 0.2	1.17 ± 0.3	0.06
LDL-C (mmol/L)	3.34 ± 1.1**	3.0 ± 0.44*	2.7 ± 0.74	0.01
Drinking history (n,%)	41 (12.8)	30 (10.7)	37 (9.7)	0.06
Region(n,%)				
City	200(62.5)▲▲	200(62.5)▲▲	294(61.25)	0.37
Country	120(37.5)	80(37.5)	186(38.75)	0.30
Education level(n,%)				
Primary school	35 (10.9)*	18 (6.42)	20 (6.6)	0.06
Secondary School	275 (85.9)▲▲	250 (89.28)▲▲	270(90)▲▲	0.35
University or high	10 (3.125)*	12(4.28)	10(3.33)	0.37
Economic status(n,%)				
poor	20 (6.25)	30 (9.38)*	16 (5.3)	0.17
Medium	260(81.25.)▲	200(71.4)	252 (84)	0.18
well-off	40 (12.5)	50 (17.85)	32 (10.6)	0.05
profession(n,%)				
Individual	230(71.8)▲▲	191(68.2)▲▲	220(73.3)▲▲	0.37
Cadre	34 (10.6)▲▲	33(11.78)▲▲	30 (10)▲▲	0.41
Doctor	7 (2.18)	6 (2.14)	5 (1.66)	0.45
Teacher	12 (3.75)	10 (3.57)	10 (3.3)	0.42
Student	37 (11.56)	40 (14.28)	35 (11)	0.35
Medications n, (%)				
Cytochrome C	300 (93.8)	276(98.6)	—	0.25
Coenzyme A	310 (96.9)	266(95)	—	0.45
CBPHI	277 (86.6)**	186(66.4)	—	0.01
Glycerol fructose	276 (86.3)	228(81.4)	—	0.44
Ulinastatin	67 (29)**	16 (5)	—	0.01
Naloxone	21 (7.5)**	9 (3.2)	—	0.01
*P < 0.05,**P < 0.01. between ICH and controls,*p<0.05,**p<0.01,between LT3 and SCH;▲P< 0.05,▲▲P < 0.01 .				

Compared with the control, the levels of serum BPA, various proteases, inflammatory cytokines and miR-338-3p on day 2 of LT3 and SCH increased, miR-455 decreased, and blood pressure parameters increased, P<0.05. The ratio of free testosterone in male patients to the control group was significantly lower P <0.01. In addition, there was no significant difference in serum rT3 and miR-144 levels between the two groups, P≥0.05, omitted. (Table 2)

Table 2
Comparison of serum BPA,biomarkers and BP scores in different gender subgroups.

Paramet	LT3				SCH			
Biomarbimarker	Male(n=240)	Control(n=240)	Female(n=80)	Control(n=80)	Male(n=80)	Control(n=80)	Female(n=200)	Control(n=200)
BPA,b BPA ng/ml (2)	0.93±0.18** ^{□□}	0.52±0.14	0.79±0.14**	0.52±0.12	0.82±0.11** [□]	0.53±0.10	0.70±0.1**	0.53±0.1
MMP-9 ,ng/ l	109±11** ^{□□□□}	47 ± 8	99±9.5**	43 ± 6	102±8.5**	43 ± 6.5	96±7.8**	43 ± 6.3
Thrombin, ng/mL	1.5±0.5**	0.65±0.1	1.31±0.49**	0.64±0.09	1.29±0.23 **	0.63±0.1	1.29±0.23**	0.66±0.12
miR-338-3p ng/mL	3.1±0.9**	1.2±0.8	2.8±0.94**	1.23±0.85	2.6±0.7**	1.2±0.51	2.53±0.6**	1.18±0.4
miR-451 ng/mL	2.62±0.17**	3.3±0.32	2.7±0.2**	3.2±0.4	2.83±0.2**	3.3±0.5	2.91±0.14**	3.22±0.6
TLR-4,ng/mL	1.41±0.21** ^{□□}	0.57±0.10	1.1±0.2**	0.57±0.09	1.22±0.2**	0.53±0.1	1.06±0.13**	0.55±0.2
MyD88,ng/mL	1.13±0.33 ** ^{□□□}	0.44±0.09	1.1±0.25**	0.52±0.1	0.92±0.1 **	0.49±0.1	0.90±0.13 **	0.45±0.1
TRAF6,ng/mL	1.64±0.41 ** ^{□□□}	0.34±0.10	1.45±0.50 ** ^{□□□}	0.33±0.09	1.42±0.44 ** ^{□□□}	0.36±0.098	1.37±0.40 ** ^{□□□}	0.35±0.09
NF-kBP 65,ng/mL	1.21±0.2** ^{□□□}	0.51±0.10	1.08±0.2**	0.50±0.08	1.0±0.2**	0.48±0.1	0.86±0.1**	0.50±0.2
FT3,pg/ml	0.74±0.2** ^{□□}	4.8± 0.8	0.86±0.5** [□]	4.8±0.9	4.17±0.7	4.33±0.6	4.2±0.5	4.8± 1.0
FT4,pmol/l	24± 7.2	30 ± 9.2	26± 9.0	31 ± 9.2	28 ± 8.6	28.5 ± 6.1	26±12.2	31± 9
T3, nmol/l	1.67 ± 1.0	2.0± 0.6	1.65 ± 0.9	2.0± 0.6	2.1 ± 0.5	2.2± 0.4	1.69 ± 1.0	2.1± 0.7
T4, nmol/l	66 ± 19.7*	85±11.4	68 ± 17.7*	85±12	78± 10.7	86±14	79± 19	85±11
TSH,μIU/ml	3.6 ± 0.4	3.7± 0.7	3.8 ± 0.6	3.7± 0.9	12.9±2.18**	3.91± 0.9	9.6±0.7**	3.7± 0.5
FT(nmol/L)	0.13±0.0**	0.21±0.05	0.20±0.06	0.21±0.05	0.15±0.05*	0.20±0.5	0.19±0.02	0.21±0.04
TT(nmol/L)	4.9±1.5**	17±4.6	16±4.2	17±4.6	7±1.4*	16±3.5	15±4.5	17±4.6
24hDBPCV (95%,interval)	0.17(0.12- 0.19)**	0.11(0.08- 0.12)	0.16(0.12- 0.19)**	0.10(0.08- 0.11)	0.14(0.07- 0.15)*	0.09(0.06- 0.10)	0.13(0.1-0.16)*	0.09(0.07- 0.11)
nDBPCV (95%,interval)	0.16(0.09- 0.19)** [□]	0.05(0.02- 0.08)	0.14(0.08- 0.17)**	0.05(0.02- 0.07)	0.13(0.07- 0.5)**	0.04(0.02- 0.06)	0.11(0.06- 0.14)**	0.04(0.02- 0.05)
5 days,n % Death rate	6 (1.875) ^{□□□□}	-	3 (0.937)	-	3 (1.07)	-	2(0.714)	-

*P < 0.05; **P < 0.01. between ICH and controls,[□]p[□]0.05,^{□□}p^{□□}0.01; between male and female,[□]p[□]0.05,^{□□}p^{□□}0.01; between LT3 and SCH.

ICH patients and the control were divided into two gender subgroups. The BPA level of ICH men increased significantly compared with women and the control, and there was also a difference between women and the control p <0.01 .(Figure 1)

LT3-male nDBPcv compared with female and control, SCH male, female compared with control group, P<0.01.(Figure 2)

Compared with the female LT3 and the control, the FT3 of the male LT3 was significantly reduced, and the female SCH group TSH was significantly increased compared with the male and the control, P<0.05 .(Figure 3)

Compared with the control, the serum BPA and protease in the LT3 and SCH groups at 15 and 30 days tended to decrease; on the contrary, the level of miR-338-3p decreased, the level of miR-455 increased, and the blood pressure parameters increased. In particular, nDBPCV was more Obviously, P <0.01. (Table 3)

Table 3
Comparison of serum bisphenol A, biomarkers and death rate in different subgroups.

1 15 day	LT3	SCH						
Bioma bi biomarer	Male (n=240)	Control(n=240)	Female(n=80)	Control(n=80)	Male(n=80)	Control(n=80)	Female(n=200)	Control(n=200)
BPA,b BPA ng/ml (2)	0.89±0.15** [□]	0.52±0.14	0.74±0.11**	0.52±0.12	0.78±0.1**	0.53±0.10	0.70±0.12**	0.53±0.1
MiR-338-3p ng/ml	1.7±0.37*	1.21±0.2	1.41±0.59*	1.22±0.55	1.25±0.56	1.22±0.49	1.22±0.46	1.21±0.49
MiR-451 ng/ml	3.4±0.19*	3.25±0.31	3.6±0.19*	3.3±0.3	3.5±0.19	3.24±0.32	3.45±0.19	3.3±0.30
Death rate n, %	4(1.25) [□]	-	2 (0.625) [□]	-	3 (1.07) [□]	-	1(0.357)	-
30 days								
BPA,b BPA ng/ml (2)	0.89±0.14** [□]	0.52±0.12	0.70±0.10**	0.52±0.11	0.73±0.12**	0.53±0.10	0.66±0.10**	0.53±0.1
MiR-338-3p ng/ml	1.42±0.3*	1.21±0.2	1.28±0.59*	1.23±0.55	1.24±0.56	1.22±0.49	1.217±0.4	1.21±0.42
MiR-451 ng/ml	3.6±0.19	3.28±0.27	3.7±0.18	3.26±0.31	3.8±0.19	3.24±0.34	3.9±0.19	3.3±0.35
Death rate n, %	20 (6.25) ^{□□□}	-	8 (1.56)	-	7 (2.5)	-	6 (2.14)	-

*P < 0.05; **P < 0.01. between ICH and controls;[□]p<0.05,^{□□}p<0.01; between male and female;[□]p<0.05,^{□□}p

<0.01; between LT3 and SCH.

There were 600 cases of ICH, and the recent total mortality rate was 74 cases (12.3%). There were 320 cases of LT3 and 50 deaths (15%); 280 cases of SCH and 24 deaths (8.57%). The recent mortality rates of the two groups were compared in 5, 15, and 30 days. 15 (4.7) vs 7(2.5), 20(6.25) vs 10 (3.75), 15(4.68) vs 7(2.5) P<0.01. (Figure 4)

On day 2, serum miR-338-3p significantly increased compared with the control, while miR-445 significantly decreased. P<0.01.(Figure 5)

On day 15 serum miR-338-3p significantly lowed compared with the control, while miR-451 significantly increased. P<0.01.(Figure 6)

Serum miR-338-3p decreased more significantly on day 30 compared with that on day 15 and the control, while miR-451 increased significantly. P<0.01. (Figure 7)

Serum BPA is positively correlated with biomarker, 24hDBPCV, and was negatively correlated LT3 and niR-451.(Table 4)

Table 4. Linear correlation analysis of serum BPA and ABP and biomarkers in YICH.

Variables			r value	P value	Variables			r value	P value
BPA	and	miR-388-3p	0.46	<0.01	BPA	and	thrombin	0.55	<0.01
BPA	and	24hDBPCV	0.48	<0.01	BPA	and	miR-451	-0.52	<0.01
BPA	and	MMP-9	0.51	<0.01	BPA	and	FT3	-0.51	<0.01

The increase of nSBP and nDBP were used as dependent variables, and age, gender, BMI and BPA were used as independent variables. The results of multiple linear regression showed that cumulative BPA exposure was an independent factor affecting of nSBP and nDBP.(Table 5)

Table 5 . Multiple linear regression analysis of nSBP and nDBP increase (n=600)

D variable	I variable	B	SE	β	t value	P value
nSBP	constant	16.432	1.939	—	7.482	< 0.01
	BPA	1.935	0.448	0.229	3.452	< 0.05
nDBP	constant	18.449	2.439	—	8.442	< 0.01
	BPA	2.335	0.398	0.286	4.452	< 0.01

The relationship between BPA, thrombin and miRNA expression risk factors: draw a BPA ROS curve, the area under the curve is 0.744 (95% CI 0.624-0.894), the maximum Uden index is 0.426, the sensitivity is 75.4%, and the specificity is 67.4%, corresponding to a cut-off value of 1.567. Adjusting for confounding factors such as gender, age, and marital status, the risk of BPA in ICH patients is 5.12 times that of the general population. (Table 6)

Table 6 Logistic regression analysis of serum bisphenol A level,blood lipid and risk factors (n=280)

Independent variable	B	SE	X ² value	P value	OR	95%CI
BPA	2.86		0.613	9.89	0.003	7.413 [0.624-0.931]
Thrombin	2.41		0.514	8.99	0.002	5.114[0.891-1.614]
miR-338-3p	1.618		0.412	12.007	0.001	4.170 (1.861-9.431)
BMI stratification normal						
Thin	-0.214		0.891	0.059	0.124	6.784 (0.129-4.718)
Overweight, obese	1.090		0.412	6.410	0.011	2.803 (1.247-6.313)
Insulin resistance index	1.214		0.539	7.140	0.009	3.143 (1.349-8.726)
High triglycerides	1.225		0.397	5.765	0.02	2.56 (1.19-4.976)
High Tch	1.231		0.497	6.476	0.01	2.948 (1.241-5.736)

Increase BPA levels (none = 0, yes = 1) and miR-451 (none = 0, yes = 1), nDBPCV (none = 0, yes = 1), binding and interaction analysis. The results of the cross-health analysis showed that after adjusting for factors such as gender, age, and marital status. Nocturnal hypertension and the low expression of miR144/451 and the presence of elevated serum BPA are significantly different from the BPA levels of patients with non-nocturnal hypertension, and there is a risk of ICH. The results of interaction analysis showed that there is a multiplicative and additive interaction between whether serum BPA is related to nocturnal hypertension (U = 4.19, P <0.05) and whether miR-451 is under-expressed (U = 6.16, P <0.05)Table 7

Table 7 Effect of BPA level on the coefficient of variation of night blood pressure (n=280)

-BPA miR-451 nDBPCV			NBP	OR	MI	AI
(n)	(n)	(n)	(n)	(95%CI)		
No	No	No	240	1.947(0.175-29.987)	0.0134	RERI:3.12(0.912-3.123)
No	No	No	1	0.765 (0.32-0.915)		AP:5.13 (0.723-1.346)
Yes	160	240	0	4.997(1.845-9.365)		S:1.715(0.541-15.57)
Yes	140	240	0	19.778(1.879-245.667)		

Discussion

Bisphenol A (BPA) is an endocrine disruptor, which not only interferes with thyroid function, but also affects sexual function. Studies have reported ^[12-14] that in stress diseases such as heart and brain, female patients are mostly at risk of SCH This study found that the serum BPA in the male group of YICH patients was significantly increased compared with the female group, and the free testosterone (FT) level in men was significantly reduced. It also shows that women

are mostly SCH, while men are mostly LT3 syndrome. It is speculated that there is a certain inherent correlation between the toxic effects of BPA exposure on the thyroid and sexual function, involving a chain of chain events.

Ambulatory blood pressure is related to target organ damage, and the circadian rhythm of blood pressure has an important influence on the pathophysiology of diseases. Studies have reported that^[15–17] BPA exposure from canned food can increase blood pressure, and blood pressure variability is involved in the occurrence and development of target organ damage^[18]. Although BPA exposure does not directly affect plasma lipid levels, it can enhance the expression of CD36 in macrophages, which is related to lipid accumulation^[19]. There are changes in oxidized protein and lipid levels in atherosclerosis^[20]. The baseline data of this study showed that the blood lipid level of YICH patients was significantly higher than that of the control, and the night diastolic blood pressure and blood pressure scores were significantly increased. In addition, multiple linear regression analysis showed that BPA is an independent risk factor that affects the percentage increase of nSBP and nDBP.

The biological trigger BPA is biochemically toxic to multiple organ functions. Exposure is related to oxidative stress, insulin resistance, and changes in microRNA (miR) expression profiles^[21, 22], defining the potential mechanism of toxic miR. miR-144/451 may be beneficial under stress conditions and has a certain protective effect on vascular endothelial function. Oxidative stress is a series of reactive oxidation, forming a series of network links from biological toxicity to cytotoxicity and lipotoxicity.

Inflammation and apoptosis are related to the prognosis and survival of patients, and the inflammatory environment can cause neuronal apoptosis^[23]. BPA exposure can induce vascular toxicity and risk events, which can gradually affect cerebrovascular pathology and molecular phenotypic biochemical factors. Nuclear factor- κ B transcription factor is a multifunctional transcription factor. The NF- κ Bp65 inflammatory pathway induces oxidative stress and apoptosis, and improves cytological functions^[24]. Inflammation, oxidative stress and other factors can cause vascular dysfunction and structural damage^[25]. Therefore, targeting TLR4 in ICH patients can attenuate the inflammatory response, thereby attenuating apoptosis and improving prognosis^[26]. The study of this group showed that serum inflammatory cytokines and TLR4-NF- κ B signaling pathway series factors were significantly increased, and the initial thrombin concentration was associated with a higher risk after stroke, indicating that the expression of ncRNA has time-point changes. It is speculated that this phenomenon is related to the treatment and the protective factors of the body's autoimmunity. This study also found that the recent mortality rate of the LT3 group was significantly increased compared with that of the SCH group, indicating the resonance of the body, which needs to be confirmed by further studies. In addition, correlation analysis showed that BPA was positively correlated with miR-338-3P and a variety of proteases, and negatively correlated with miR-451.

The main limitation of this study is the lack of analysis and research on the relationship between the drug and BPA biotoxicity and biomarkers. In-depth analysis of the anti-inflammatory, network homeostasis and neuroprotective effects of connexin 43 after ICH injury is required. Clarify the innervation or position of β 3 adrenergic nerves, and target the adrenergic system to effectively inhibit the neuroinflammatory mechanism after ICH

Conclusion

High BPA exposure strongly predicts the risk of YICH patients. Activation of NF- κ B signaling pathway, secondary thyroid function and ABP changes, together to construct an inflammatory response program, is related to the risk of short-term death.

Declarations

Availability of data and materials

The de-identified dataset generated and analyzed in this study is electronically stored and protected by specific password. The dataset is available from the corresponding author on reasonable request.

Acknowledgements

Thanks to Professor Wu Bowei ,Zhang Mingshen and some teachers, residents, students of Shanxi Medical University

Funding

This work was supported by the Natural Science Foundation of Shanxi Province (grant no. 201701D121177); Shanxi Science,Technology Department of the Project Fund (2011099); Spark Planning Project of Changzhi (200704009).

Author contributions

Dr GPW responsible for the writing of the first draft and collection and preservation of some specimens; Prof,DG undertake specimen testing and data analysis;Drs LF Z,LL Z, AVW,CPF recruited eligible patients and collected the blood sample;Drs PG, undertook to follow up ;Dr WLS recruited and analysis CT and MRI data;all authors contribute to the subsequent draft ;Dr GPW,JYL,ZDQ and Drs **JHC**, conducted study design and manuscript revisio.

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Ethics declarations

Ethics approval and consent to participation

All methods in this study were performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Changzhi People's Hospital affiliated with Shanxi Medical University (No: 2013093). All data obtained from the Changzhi research database have been de-identified, and all patients have the right to know the project and sign an informed consent form.

Consent for publication

Not applicable.

Competing interests

The authors declare that there was no conflicts of interest.

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Figures

Figure 1. Serum BPA levels in YICH patients and controls,as well as in male and female subgroups..(a, b)

Figure 1

Serum BPA levels in YICH patients and controls,as well as in male and female subgroups..(a, b)

Figure 2. nDBPCV levels in YUICH and control

Figure 2

nDBPCV levels in YUICH and control

Figure 3 :Comparative analysis of ICH thyroid function of different genders and control group (a,b)

Figure 3

Comparative analysis of ICH thyroid function of different genders and control group [a,b]

Figure 4: Comparison of mortality between the LT3 and SCH groups

Figure 4

Comparison of mortality between the LT3 and SCH groups

Figure 5, Comparison of miR-338-3p ,miR-451 levels in the two groups (2 days. a,b, c,d)

Figure 5

Comparison of miR-338-3p ,miR-451 levels in the two groups (2 days. a,b, c,d)

Figure 6 : Comparison of serum miR-338-3p and miR-451 levels in the two groups

(For 15. a,b,c,d)

Figure 6

Comparison of serum miR-338-3p and miR-451 levels in the two groups [For 15. a,b,c,d]

Figure 7 : Comparison of serum miR-338-3p and miR-451 levels in the two groups
(For 30 .-a,b,c,d)

Figure 7

Comparison of serum miR-338-3p and miR-451 levels in the two groups [For 30 .-a,b,c,d]

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