Characteristics of Endocrine Metabolism in AL Amyloidosis Patients

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Abstract

Background To explore characteristics of thyroid gland and glucose metabolism in light chain (AL) amyloidosis patients.

Methods A total of 20 amyloidosis patients were recruited. Thyroid function and biochemical indices were tested. Intravenous glucose tolerance test was performed in all patients. Thyroid ultrasound was also determined.

Results 1.There was 7 patients with hypothyroidism (35%) and 4 patients with subclinical hypothyroidism (20%). Additionally, a total of 6 patients manifested as euthyroid sick syndrome (30%); 2. A number of 15 patients showed thyroid nodule (75%); 3. The fast blood glucose was 4.85±0.8 mmol/l. The level of blood glucose after intravenous glucose tolerance test showed 8.03±1.88 mmol/l at 30 minutes and 7.1±3.22 mmol/l at 120 minutes. 4. The blood insulin levels in fasting, 30 minutes and 120 minutes were 5.2±2.59 mIU/L, 308.3±199.4 mIU/Land 245.66±176.44 mIU/L. Further, the values of C-peptide showed 2.47±1.43 ng/ml, 6.74±3.16 ng/ml and 8.98±4.83 ng/ml. Homeostasis model assessment of insulin resistance and Homeostasis model assessment of β cells of the patients were 1.2±0.62 and 88.45±46.17, respectively. There were 2 patients diagnosed with diabetes and 1 patient with impaired glucose tolerance.

Conclusions AL amyloidosis patients revealed high prevalence of hypothyroidism, subclinical hypothyroidism and euthyroid sick syndrome. However, glucose metabolism showed no influence in amyloidosis patients.

Background

Light chain (AL) amyloidosis is a disorder of protein fold leading to dysfunction of organs resulting from extracellular deposition of immunoglobulin light chains. The prevalence of AL amyloidosis is minimum 8 per million [1]. However, outcome of AL amyloidosis is severe with 40% one-year mortality [2]. The death of AL amyloidosis is mainly attributed to cardiac involvement. Apart from the myocardiopathy induced by AL amyloidosis, kidney, liver, bone marrow and skin are also common implicated organs. Compared with international consensus creteria, ^{18}F-florbetapir PET/CT has revealed greater numbers of organs with amyloid deposition [3]. It has been reported that endocrine gland [4] may be influenced by AL amyloidosis which may be neglected clinically. As diagnosis of AL amyloidosis is based on pathology, the involvement of islet is not available to receive biopsy without obvious symptoms which also can not be assessed by radiologic features. In parallel, thyroid gland deposition of amyloid protein lacks clinical assessment methods resulting in 5 patients involved with Thyroid gland but only one case was clinical suspicious by PET/CT which gives a significant deposition assessment in amyloidosis patients[5].

Previous study has indicated that a markedly number of AL amyloidosis patients manifested as hypothyroidism [6]. However, case report showed unaltered thyroid function but presented with a nodule by ultrasound which eventually was diagnosed as AL amyloidosis [7]. Therefore, mere thyroid function

determination is insufficient to assess whether thyroid gland has been involved. Meanwhile, no data to date are available about the characteristics of glucose metabolism in AL amyloidosis. In present study, we assessed endocrine metabolism including thyroid gland and glucose metabolism to describe endocrine characteristics of AL amyloidosis patients.

Materials

A total of 20 patients hospitalized with AL amyloidosis from January 2018 to July 2019 were registered via case records system from Sir Run Run hospital. Subjects who were younger than 18 years old, fever, women who were pregnant and patients with acute kidney injury were excluded. Intravenous glucose tolerance test with 75 g glucose was performed in all patients and blood samples were collected at fast time, 30 minutes after injection and 120 minutes after injection.

Laboratory Measure

Serum creatinine (sCr) , cystatin C, uric acid, β2microglobin, serum albumin, serum lipid and proteinuria were measured by Roche Cobas 8000 c701 via immunoturbidimetry. Hemoglobin (Hb) was detected by SYSMEX XN-B2 via Flow cytometry assay. Glycated hemoglobin (HbA1c), insulin, C-peptide, thyroid function were determined using Roche Cobas 8000 c602 via electrochemiluminescence. The values of serum immunoglobulin and complement were measured by singe immunodiffusion.

Definitions

1. AL amyloidosis was defined via renal biopsy and involved organ was assessed based on consensus criteria [8].
2. CKD stages were defined in accordance with KIDGO guideline: stage 1, estimated glomerular filtration rate (eGFR) ≥90ml/min/1.73m2; stage 2, 60 ml/min/1.73m2 ≤ eGFR < 90 ml/min/1.73m2; stage 3, 30 ml/min/1.73m2 ≤ eGFR < 60 ml/min/1.73m2; stage 4, 15 ml/min/1.73m2 ≤ eGFR < 30 ml/min/1.73m2; stage 5, eGFR < 15 ml/min/1.73m2. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKDEPI) fourlevel race equation [9,10] and the last sCr value before discharge was selected as the baseline level. The specific CKDEPI fourlevel race GFR estimation equation was as follows:

eGFR =EXP(LN(151) 0.328 * LN(sCr/88.4/0.7) + age * LN(0.993)) (If female and creatinine <0.7);

=EXP(LN(151) 1.210 * LN(sCr/88.4/0.7) + age * LN(0.993)) (If female and creatinine >=0.7);

=EXP(LN(149) 0.412 * LN(sCr/88.4/0.9) + age * LN(0.993)) (If male and creatinine <0.9);

=EXP(LN(149) 1.210 * LN(sCr/88.4/0.9) + age * LN(0.993)) (If male and creatinine >=0.9).

3. Thyroid nodule was diagnosed based on the presence of a characteristic ultrasound pattern by an experienced sonographer blinded to patients' clinical and laboratory data. The study image was then analyzed by another sonographer which was also blinded to patients' clinical and laboratory data and the final assignment was confirmed by the 2 operators.
4. Homeostasis model assessment of insulin resistance (HOMA-IR) = fast Insulin (mU/L)×fast blood glucose (FBG) (mmol/L)/22.5. Homeostasis model assessment of β cells (HOMA-β) = 20* fast Insulin /(FBG-3.5).

Statistical analysis

Statistics analysis was performed by PASW 18.0 statistical software (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± SD. χ^2-test was performed to calculate frequency of thyroid nodule.

Results

1. Clinical characteristics of AL amyloidosis patients （Table 1）

There were 20 patients were enrolled. The values of clinical indices were shown in table 1. The level of free triiodothyronine was 3.48 ± 0.78 pmol/l, total triiodothyronine 1.47 ± 0.54 nmol/l, free thyroxine 12.82 ± 2.87 pmol/l and total thyroxine 74.09 ± 23.92 nmol/l. The level of thyroid stimulating hormone was 4.43 ± 2.57 mIU/l. The value of albumin was 29.61 ± 9.98g/l. The eGFR was 70.5 ± 36.5ml/min*1.73m^2.

Table 1
Clinical characteristics of monoclonal immunoglobulin related renal syndrome patients

	Minimum	Maximum	Mean	SD
body mass index, kg/m^2	18.92	29.86	23.57	3.0
thyroid stimulating hormone, mIU/l	0.58	9.71	4.43	2.57
free thyroxine, pmol/l	7.77	19.98	12.82	2.87
thyroxine, nmol/l	8.5	125.9	74.09	23.92
free triiodothyronine, pmol/l	2.14	4.77	3.48	0.78
triiodothyronine, nmol/l	0.89	3.51	1.47	0.54
white cells counts, 10^^{9}	4.03	15.4	7.58	2.75
erythrocyte cells, 10^^{12}	2.34	4.52	3.74	0.63
hemoglobin, g/l	81	144	115.6	18.34
platelet, 10^^{12}	116	330	194.9	64.29
glutamic-pyruvic transaminase, U/L	8	38.2	16.4	7.23
glutamic oxalacetic transaminase, U/L	11.2	66.7	20.66	11.51
albumin, g/l	16.9	50.4	29.61	9.98
total cholesterol, mmol/l	2.8	11.6	5.97	2.18
triglyceride, mmol/l	1.3	6.2	2.43	1.16
blood urea nitrogen, mmol/l	2.6	20	7.93	3.49
uric acid, umol/l	103.7	443.5	286.62	78.96
serum creatinine, umol/l	50	513	126.63	122.15
eGFR, ml/(min*1.73 m^2)	7.66	125.44	70.5	36.5

2.The blood glucose metabolism of monoclonal immunoglobulin related renal syndrome patients (Table 2)

The FBG was 4.85±0.8 mmol/l. The level of blood glucose after intravenous glucose tolerance test showed 8.03±1.88 mmol/l at 30 minutes and 7.1±3.22 mmol/l at 120 minutes. The blood insulin levels at fasting, 30 minutes and 120 minutes were 5.2±2.59 mIU/L, 308.3±199.4 mIU/L and 245.66±176.44 mIU/L. Further, the values of C-peptide showed 2.47±1.43 ng/ml, 6.74±3.16 ng/ml and 8.98±4.83 ng/ml. In addition, insulin resistance index and sensitive index were assessed with HOMA-IR and HOMA-β with

the value of 1.2±0.62 and 88.45±46.17, respectively. There were 2 patients diagnosed with diabetes and 1 patient with impaired glucose tolerance.

3. Thyroid metabolism status of AL amyloidosis patients (Table 3)

Table 2
glucose metabolism of monoclonal immunoglobulin related renal syndrome patients

	Minimum	Maximum	Mean	SD
fast blood glucose, mmol/l	3.98	7.02	4.85	0.80
post prandial glucose 30mins, mmol/l	6.31	12.9	8.03	1.88
post prandial glucose 120mins, mmol/l	4.17	17.46	7.1	3.22
fast-insulin, mIU/L	1.7	12.09	5.20	2.59
insulin30mins, mIU/L	57.65	782.1	308.3	199.4
insulin120mins, mIU/L	20.92	576.4	245.66	174.26
fast c-peptide, ng/ml	1.1	7.57	2.47	1.43
c-peptide 30min, ng/ml	2.72	11.89	6.74	3.16
c-peptide 120min, ng/ml	2.45	19.47	8.98	4.83
Homeostasis model assessment of insulin resistance	0.27	2.87	1.20	0.62
Homeostasis model assessment of β cells	10.96	199.39	88.45	46.17

There was 7 patients with hypothyroidism (35%) and 4 patients with subclinical hypothyroidism (20%). Additionally, a total of 6 patients manifested as euthyroid sick syndrome (30%). Furthermore, 15 patients showed thyroid nodule (75%).

Table 3
thyroid function of monoclonal immunoglobulin related renal syndrome patients

	frequency
hypothyroidism	7(35%)
Subclinical hypothyroidism	4(20%)
ESS	6(30%)
Thyroid nodule	15(75%)

Discussion

Our study performed characteristics of thyroid gland and β-cell function in AL amyloidosis patients. Thyroid function showed that high level of hypothyroidism, euthyroid sick syndrome and subclinical hypothyroidism. Unexpectedly, the prevalence of thyroid nodule was as high as 75 percent. In addition, only two patients were diagnosed with diabetes via intravenous glucose tolerance test and the β-cell function revealed normal basic insulin secretion level and sufficient postprandial response.

AL amyloidosis has been reported to be involved in endocrine gland, such as pituitary gland [11], adrenal failure [12], thyroid gland [13,14]. The involvement of thyroid gland manifested as hypothyroidism and goiter [6,15-16]. As goiter can also be induced by hypothyroidism, it should be defined via thyroid gland biopsy to determine amyloidosis induced goiter. However, using fine needle aspiration biopsy gave a rather low positive amyloidosis deposition frequency which could be ameliorated by the pathology of subtotal thyroidectomy [17]. Therefore, few studies reported the amyloidosis induced goiter manifestation. Based on the above facts, abnormality of thyroid gland were often neglected in amyloidosis patients. Previous study [6] has shown a big prevalence of hypothyroidism which was similar to our study. However, our study revealed higher frequency of hypothyroidism than the result shown before which exhibited higher subclinical hypothyroidism [6]. In addition, we have previous indicated euthyroid sick syndrome is a common syndrome in CKD patients with more than 54% prevalence [18] which has been indicated similar frequency in amyloidosis in a review paper [19]. However, in amyloidosis patients of our study, the frequency revealed 30% which was lower than before attributed to more patients developed hypothyroidism. Although AL amyloidosis manifested as goiter, the previous studies were case reports. No data to date are available about the prevalence of thyroid nodule in our knowledge. In our study, we showed high frequency of thyroid nodule which was beyond our expectation. We speculated that hypothyroidism and amyloidosis both contributed to the phenomenon which should be verified via pathology. Nevertheless, our study gave an important remind of focusing on thyroid image in AL amyloidosis patients.

Apart from thyroid gland, we also explored whether islet function was involved. It is common that islet amyloid polypeptides deposit in islet which contributes to the pathogenesis of type 2 diabetes [20,21]. AL amyloidosis is rare to be reported to influence islet. There were only some case reports about the infiltration of amyloidosis stained with positive congo red and enlargement of islet [22,23]. Although islet was involved, no diabetes or hyperglycemia was presented which might be neglected clinically. In our study, we revealed only 2 patients diagnosed with diabetes which is similar to prevalence of type 2 diabetes in China. Additionally, islet function also exhibited no difference between amyloidosis patients and healthy populations suggesting normal glucose metabolism for this kind of patients.

There are some limitations in our study. First, there was only 20 patients in our study which may give a size bias. Because the study was focused in one hospital and the prevalence of Al amyloidosis is pretty low. Therefore, it is difficult to accumulate big size study to explore the metabolism status of AL amyloidosis patients which need further study to give more solid evidence. Second, lacking of pathology

data will limit diagnosis of organ involvement. As the recruited patients reveled no significant organ related symptoms which may limit the biopsy of thyroid. Furthermore, islet biopsy is difficult to fulfill unless abnormality of nodule by radiography. Nevertheless, thyroid nodule biopsy in AL amyloidosis may be available in future to assess the involvement of the organ.

Conclusions

Taken together, our study revealed the characteristics of islet and thyroid gland in AL amyloidosis patients. Thyroid nodule and dysfunction of thyroid function were common in AL amyloidosis patients suggesting attention should be focused on assessing radiography of AL amyloidosis patients.

Abbreviations

Light chain (AL), estimated glomerular filtration rate (eGFR), serum creatinine (sCr), Hemoglobin (Hb), glycated hemoglobin (HbA1c), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Homeostasis model assessment of insulin resistance (HOMA-IR), Homeostasis model assessment of β cells (HOMA-β), fast blood glucose (FBG).

Declarations

-Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Nanjing medical university, Sir Run Run hospital. Written consent received from patient was written informed consent for participation in this study.

- Consent to publish

All authors agree to submit.

-Availability of data and materials

The data supporting the conclusions of this article is available by emailing to panbinbin@njmu.edu.cn.

-Competing interests

The authors have nothing to disclose.

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-Authors' contributions

The research was designed by B.P., and C.C. All authors helped to write the report and commented on the manuscript. B.P. analyzed the data and advised on statistical issues at the time of the research write-up. C.C. was the research administrator, obtained the data, and prepared communications with participating centers and the data monitoring committee. F.F.C. and X.W. were research nurses responsible for recruitment and return of data.

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-Authors' Information

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