Clinical and pathological analysis on Traditional Chinese Medicine syndromes in children with immunoglobulin A nephropathy

Xue Shi, Nan Zhou, Chunju Zhou, Ying Shen

Abstract

OBJECTIVE: To evaluate the common Traditional Chinese Medicine (TCM) syndromes and analyze their relationship to clinical and pathological manifestations in children with IgA nephropathy.

METHODS: Forty five children diagnosed as having primary IgA nephropathy by renal biopsy for the first time were enrolled in this trial, and their TCM syndromes were evaluated and the distribution of TCM syndromes was observed. All the sick children were grouped according to clinical manifestations and pathological damages, and the differences in TCM syndromes were compared between the groups.

RESULTS: The first 5 TCM symptoms were common cold, hyperhidrosis, red dry throat, dark yellow urine and lassitude. In the acute nephritis group, edema and aching pain in loin and knees were significant \((P=0.021\) and \(P=0.000)\). In the severe pathological damage group, edema was obvious \((P=0.004)\), and 24 h urinary protein was positively correlated with edema \((P=0.015)\) while negatively with common cold \((P=0.007)\). The score of mesangial cell proliferation was correlated with edema, red dry throat and common cold \((P=0.006, 0.013\) and \(0.029\) respectively). The score of segmental pathological change was positively correlated with edema \((P=0.039)\).

CONCLUSION: Common cold, hyperhidrosis, red dry throat, dark yellow urine, lassitude and other symptoms of qi deficiency of the spleen and lung mainly seen in children with IgA nephropathy may bear a close relationship to clinical manifestations and pathological damages.

Key words: Glomerulonephritis, Immunoglobulin A; Children; Urination disorders; Qi deficiency of spleen and lung

INTRODUCTION

IgA nephropathy, one of the commonest primary glomerulopathies leading to chronic kidney failure, has an unoptimistic prognosis with the disease developing into nephropathy at terminal stage in 20%-40% of adult patients 20 years after onset and into chronic kidney failure in 10%-30% of child patients 15-20 years after onset.\(^1\)\(^2\)

At present, combination of TCM and Western medicine may be helpful to prove the prognosis IgA ne-
phropathy. It is important to standardize the syndrome differentiation and typing. Because researches have mainly concentrated on adults, TCM syndrome differentiation and typing in child patients are rarely analyzed. In fact, children are subject to diseases with their syndrome characteristics incompletely identical to adults. We selected 45 children with IgA nephropathy in our hospital and analyzed their characteristics of TCM syndromes and relations of TCM syndromes to clinical and pathological manifestations so as to provide reference for treating child IgA nephropathy and standardizing the evaluation of curative effect in the future. The protocol was in conformity with the ethics principle and approved by the ethics committee in our hospital. The informed consents were obtained for all participants.

**METHODS**

**Targets of research**

45 children diagnosed as having primary IgA nephropathy newly in the medical department of our hospital from February 2008 to July 2010 were enrolled in the trial. All the patients conformed to the diagnostic standard for IgA nephropathy in Western medicine, namely, the specimen of renal biopsy revealed evidence of immune complex deposit mainly with IgA in mesangium area. Exclusive standards were as follows: secondary IgA nephropathy, such as nephritis related to hepatitis B virus and nephritis related to allergic purpura, obvious dysfunction of other important internal organs, renal dysfunction (doubled level of creatinine), and treatment with hormone or immune inhibitor for more than 4 weeks. In clinical manifestations solitary hematuria type were found in 17 cases (37.78%), hematuria and proteinuria type in 18 cases (40.0%), acute nephritis syndrome in 4 cases (8.89%) and nephropathy type in 6 cases (13.33%). Pathological classification was as follows: 1 case of Lee class 1, 29 cases of Lee class 2, 14 cases of Lee class 3 and 1 case of Lee class 4.

**Methods of research**

Evaluation of TCM syndromes: In reference to the Guiding Principles for Clinical Study of New Chinese Medicine for Treatment of Chronic Nephropathy and according to children’s characteristics, we selected 10 out of 16 symptoms for research, namely, common cold, hyperhidrosis, dry red throat, dark yellow urine, gastric distension, anorexia, lassitude, aching pain in loin and knees, edema and sallow complexion, and divided them into 0-3 score, as shown in Table 1. Comparison of differences in TCM syndromes changed by different pathologies: We used Lee classification for pathological evaluation and Katafuchi score standard for evaluating renal pathology. For mesangial cell proliferation, score 1 means no proliferation, score 2 means mild proliferation (<25%), score 3 means moderate proliferation (25%-50%) and score 4 means severe proliferation (>50%). For segmental glomerulopathy, such as crescent formation, saccular wall adhesion, segmental sclerosis and fibrinoid necrosis of capillary wall, score 0 means no segmental glomerulopathy, score 1 means segmental glomerulopathy <10%, score 2 means segmental glomerulopathy 10%-25%, score 3 means segmental glomerulopathy 25%-50%, and score 4 means segmental glomerulopathy >50%. For interstitial fibrosis and atrophy of renal tubules, score 0 means no fibrosis and atrophy, score 1 means fibrosis and atrophy <25%, score 2 means fibrosis and atrophy 25%-50%, and score 3 means fibrosis and atrophy >50%. Comparison of differences in TCM syndromes with different clinical manifestations: Clinical manifestations referred to the clinical typing in the guide to clinical practice of IgA nephropathy, and urinary protein was recorded in 24 h.

**Statistical process**

SPSS11.0 statistical software was used. T test of independent samples or analysis of variance was used for comparison of measurement data between groups. Multiple gradual regression was used for correlation analysis.

### Table 1 Main standards for scoring clinical TCM symptoms

<table>
<thead>
<tr>
<th>TCM symptoms</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common cold (year)</td>
<td>No</td>
<td>Respiratory tract infection for 2-3 times</td>
<td>Respiratory tract infection for 4-6 times</td>
<td>Respiratory tract infection for ≥7 times</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>No</td>
<td>After obvious motion</td>
<td>After slight motion</td>
<td>At calm time</td>
</tr>
<tr>
<td>Red dry throat</td>
<td>No</td>
<td>Slightly red dry throat</td>
<td>Red dry throat</td>
<td>Obviously red dry throat</td>
</tr>
<tr>
<td>Dark yellow urine</td>
<td>No</td>
<td>Yellow urine</td>
<td>Crimson urine</td>
<td>Dark yellow urine</td>
</tr>
<tr>
<td>Gastric distension</td>
<td>No</td>
<td>Slight gastric distension which can be tolerated</td>
<td>Gastric distension can be alleviated when the stomach is empty</td>
<td>Gastric distension cannot be alleviated all day long</td>
</tr>
<tr>
<td>Anorexia</td>
<td>No</td>
<td>Appetite reduces by no more than 25%</td>
<td>Appetite reduces by 25%-50%</td>
<td>Appetite reduces by more than 50%</td>
</tr>
<tr>
<td>Lassitude</td>
<td>No</td>
<td>Occasional slight fatigue</td>
<td>Fatigue in general motion</td>
<td>Fatigue at rest</td>
</tr>
<tr>
<td>Aching pain in loin and knees</td>
<td>No</td>
<td>Felt occasionally or after overwork</td>
<td>Dull pain can be alleviated at rest</td>
<td>Obviously felt pain can not be alleviated even at rest</td>
</tr>
<tr>
<td>Edema</td>
<td>No</td>
<td>Faintly seen edema in eyelids after getting up in the morning</td>
<td>Edema in eyelids and lower limbs where hollow exists when pressed</td>
<td>Edema in the whole body where deep hollow exists when pressed</td>
</tr>
</tbody>
</table>

Figure 1 Scores of TCM symptoms
RESULTS

Score and distribution of clinical TCM symptoms
Judging from analyzing the distribution of TCM symptoms of children with IgA nephropathy, the 10 selected symptoms could well reflect their clinical illness condition, more than 70% of patients had the 5 symptoms of common cold, hyperhidrosis, red dry throat, dark yellow urine and lassitude, and 91.1% (41/45) of patients had the symptom of hyperhidrosis. In addition, in order to further evaluate the frequency or extent of every symptom, we added the scores of every symptom to get a total score as an index. The results showed that common cold and hyperhidrosis had the highest total score, followed by red dry throat, lassitude, dark yellow urine and aching pain in loin and knees, as shown in Figure 1.

Score of TCM symptoms and analysis of clinical manifestations
There was no significant difference ($P=0.164$) in the score of TCM symptoms between groups. However, there was an significant difference in the score of lassitude ($P=0.021$) and aching pain in loin and knees ($P=0.000$) between the group of acute nephritis and the other groups (Figure 2).

Table 2 shows that 24h urinary protein is positively correlated to edema ($P=0.015$) and negatively correlated to common cold ($P=0.007$).

TCM symptom scores and pathological damages
We divided the patients into a group of Lee I + II class and a group of Lee III + IV class and compared the scores of TCM symptoms between the two groups with different pathological damages. The result showed that there was no significant difference ($P=0.536$) in total score of symptoms between the two groups except edema ($P=0.004$). However, a faint tendency can be observed from Figure 3 in which the scores of lassitude, aching pain in loin and knees, edema, sallow complexion and other symptoms for yang deficiency of the spleen and kidney in the group of Lee III + IV class were higher than those in the group of Lee I + II class. Analyses of relations between renal pathological changes and TCM symptoms indicated that the score of mesangial cell proliferation is related to edema, red dry throat and common cold (Table 3) and there was significant positive correlation ($P=0.039$) between the score of segmental pathological change and edema. However, no correlation was found between interstitial fibrosis of renal tubules and TCM symptoms.

Table 2 Relations between 24h urinary protein and TCM symptoms

<table>
<thead>
<tr>
<th>TCM symptoms</th>
<th>B</th>
<th>SE</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>458.3</td>
<td>179.9</td>
<td>2.547</td>
<td>0.015</td>
</tr>
<tr>
<td>Common cold</td>
<td>-312.7</td>
<td>109.6</td>
<td>-2.851</td>
<td>0.007</td>
</tr>
<tr>
<td>Constant</td>
<td>1063.3</td>
<td>187.8</td>
<td>5.659</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Notes: SE: Standard Error.

Table 3 Analysis of relations between mesangial cell proliferation and TCM symptoms

<table>
<thead>
<tr>
<th>TCM symptoms</th>
<th>B</th>
<th>SE</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>0.385</td>
<td>0.133</td>
<td>2.901</td>
<td>0.006</td>
</tr>
<tr>
<td>Red dry throat</td>
<td>0.275</td>
<td>0.106</td>
<td>2.598</td>
<td>0.013</td>
</tr>
<tr>
<td>Common cold</td>
<td>-0.185</td>
<td>0.082</td>
<td>-2.266</td>
<td>0.029</td>
</tr>
<tr>
<td>Constant</td>
<td>2.016</td>
<td>0.182</td>
<td>11.088</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Notes: SE: Standard Error.
DISCUSSION
In this research, we mainly observed the tendency of distribution of TCM symptoms in children with IgA nephropathy and the relationship between TCM symptoms and clinical pathology. In modern medicine, the pathogenesis of IgA nephropathy, one of the common primary glomerulopathies, has not been known completely, and there has been no specific treatment of the disease so far. TCM attaches importance to diagnosis and treatment of diseases according to the nature and law of their generation, development and change. The treatment of IgA nephropathy with TCM can effectively decrease the excretion of urinary red cells and protein and improve pathological structure of the kidney. The treatment of IgA nephropathy with the combination of TCM and Western medicine may become a tendency.

Rich experience has been accumulated in the treatment of adult IgA nephropathy, and good curative effect could be achieved according to its clinical manifestation, disease classification and pathological change. Adult IgA nephropathy can be divided into the 4 types of Qi deficiency of the spleen and lung, deficiency of both Qi and yin, yin deficiency of the liver and kidney, and z deficiency of the spleen and kidney, or into types of impairment of collaterals by wind and heat, damp-heat in lower jiao, accumulation of both heat and stasis, internal heat due to yin deficiency, Qi deficiency of the spleen and kidney, deficiency of both Qi and yin, yang deficiency of the spleen and kidney, and deficiency of both yin and yang. TCM considers IgA nephropathy as a disease of "deficiency in origin and excess in superficiality" mainly with Qi deficiency and yin deficiency in origin and blood stasis and damp-heat in superficiality. Deep research into syndrome differentiation and typing is beneficial to standardizing the judge of illness condition and curative effect.

Using the method of randomly dividing groups, we observed the curative effect of combination of TCM and Western medicine on IgA nephropathy in children from 2008 to 2010. The result indicated that both combination of TCM and Western medicine and conventional therapy can effectively improve clinical symptoms and decrease urinary protein and red cells.

Through the evaluation of the 10 TCM symptoms of common cold, hyperhidrosis, red dry throat, dark yellow urine, gastric distension, anorexia, lassitude, aching pain in loin and knees, edema and sallow complexion, we have found that most symptoms have high total score, the 5 symptoms of common cold, hyperhidrosis, red dry throat, dark yellow urine and lassitude have total score, indicating that in child patients, the symptoms of Qi deficiency in the lung, spleen and kidney are mainly seen and accompanied by pathogenic excess and damp-heat, and symptoms of yang deficiency of the spleen and kidney are rarely seen. Having analyzed the TCM symptoms of 1016 patients with IgA nephropathy (including 148 patients under 19 years old), Chen Xiangmei and others have found the first 10 TCM symptoms are aching pain in loin and knees, Qi deficiency, lassitude, common cold, dizziness and tinnitus, dry mouth and throat, red painful throat, spontaneously perspiration and night sweating, dysphoria with feverish sensation in chest, palms and soles, and sallow complexion, indicating that IgA nephropathy is a disease of deficiency in origin and excess in superficiality mainly with Qi deficiency and yin deficiency in origin and blood stasis and damp-heat in superficiality. The above-mentioned research is similar to ours in that Qi deficiency of the lung, spleen and kidney accompanied by damp-heat is mainly seen in children or young people, and with the increase in age, Qi deficiency of the spleen and lung decreases while yang deficiency of the spleen and kidney gradually increases. In our research, child patients mainly had hematuria or (complicated with) non-nephropathy proteinuria, their renal function was mostly normal, and pathological damage mainly concentrates on Lee I - III class. Therefore, mild illness condition is mainly in the stage of Qi deficiency, while the above-mentioned research mainly involved adult patients with severe illness condition.

TCM symptoms are related to pathological changes. The severer the pathological damage is, the more easily the symptom of yang deficiency in the spleen and kidney will be manifested. There was no obvious deference in TCM symptoms between groups in our research. In the group of acute nephritis, the scores of aching pain in lion and knees and lassitude obviously...
increased, indicating that the symptom of deficiency of the spleen and kidney was remarkably outstanding. Due to less cases of acute nephritis, deviation may exist. Therefore, it is necessary to further expand samples for deep research. Urinary protein is one of the independent dangerous factors closely related to prognosis. Our research shows that 24 h urinary protein has a remarkably positive correlated with edema, indicating that the severer the illness condition is, the more outstanding the symptom of renal yang deficiency will be. This result is similar to that of research into adult patients. The analysis carried out by Xiangmei CHEN and others on 1016 cases of IgA nephropathy has shown that 24 h urinary protein of patients with yang deficiency of the spleen and kidney is obviously higher than that of patients with other syndromes, such as Qi deficiency of the spleen and lung, deficiency of both Qi and yin, and yin deficiency of the liver and kidney. 

Our research has shown that 24 h urinary protein is negatively correlated with common cold. We think that with the progress of illness condition, common cold and other symptoms of Qi deficiency are not main factors leading to progress of illness condition but easily infective factors for the disease. With the development of renal damage, the symptoms of yin deficiency or deficiency of both Qi and yin will gradually appear. Researches have indicated that pathological damages are related to TCM symptoms to some extent. 

Pathological changes of Qi deficiency of the lung, spleen and kidney and deficiency of both Qi and yin are mainly manifested in proliferation. Pathological change of yang deficiency of the spleen and kidney is mainly manifested in sclerosis. The degree of glomerular segmental damage in IgA nephropathy patients with deficiency of both Qi and yin is severer than that of Qi deficiency of the lung (spleen) and kidney. In the process from Qi deficiency of the lung (spleen) and kidney to deficiency of both Qi and yin, aggravation of glomerular segmental damage may be the mainly manifestation in renal pathological change. In our study the results indicated that with the gradual aggravation of pathological damage, the scores for yang deficiency of the spleen and kidney manifested in aching pain in loin and knees, lassitude, edema and sallow complexion increase. Mesangial cell proliferation and segmental damage were related to different symptoms. The result is identical to that of previous researches. In our research, due to mild pathological damage in selected child patients, TCM symptoms and damage to renal tubules can not be well evaluated, which should be further observed and studied in the future. To sum up, we have preliminarily explored the manifestation and law of TCM symptoms of children with IgA nephropathy, further analyzed the relationship between clinical manifestation and TCM symptoms and gained some preliminary conclusions. However, because of some limitations, such as less cases and imbalanced distribution of illness condition, the research only partially reflects syndrome differentiation and typing as well as the tendency of their changes. In the future, the combination of TCM and Western medicine may become an ideal selection for treating IgA nephropathy in children. It is still necessary to carry out high quality researches with more samples and in multiple centers so as to well evaluate TCM syndrome differentiation and typing in child patients.

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