Nephrotic Syndrome in Japan

Yasushi Ueda, M.D.
Professor and Chairman
The Second Department of Internal Medicine,
The Jikei University School of Medicine, Tokyo
Director of the Japanese Society of Internal Medicine

The purpose of this article is to review the current status of research on the nephrotic syndrome in Japan. In this country, there are two study groups for the nephrotic syndrome and a systematic research is now underway. One of these study groups is the Research Council for the Treatment of Adult Nephrotic Syndrome in Japan, which initiated a study in 1968 mainly by investigators in the field of internal medicine, and the other is the Nephrotic Syndrome Research Committee based on the Research Grant for Specific Diseases from the Ministry of Health and Welfare. The latter group consists of researchers in the field of epidemiology, internal medicine, pediatrics, and pathology, and it has conducted a continuous study from 1973.

From abundant research activities of these two groups, I wish to describe here only the epidemiological and therapeutic aspects of the nephrotic syndrome in Japan. In order to provide as objective and accurate data as possible, these groups established the diagnostic criteria (Table 1).

EPIDEMIOLOGICAL STUDY

The results of epidemiological studies of the nephrotic syndrome in Japan are based on data amassed by the Nephrotic Syndrome Research Committee.

Morbidity:

A nation-wide research of patients with nephrotic syndrome revealed that the overall prevalence rate is 30 children and 15 adults each per 100,000 population. It follows that an estimated 7,500 to 8,800 children and 11,300 to 15,000 adults are presumed to have the disease in the entire nation. These figures total 18,800 to 23,800 and thus the number of patients with the nephrotic syndrome in Japan is roughly 20,000, which corresponds to 0.018% of the total population.

Difference in morbidity among territories:

The incidence and morbidity rates for nephrotic syndrome among inhabitants of

Reprint requests to: Yasushi Ueda, Professor and Chairman, Department of Medicine, The Jikei University School of Medicine, 3–23–8 Nishishinbashashi, Minato-ku, Tokyo 105, Japan.
Table 1. Diagnostic Criteria for Nephrotic Syndrome.

(I) Nephrotic Syndrome in adult
1. Proteinuria: Persistent proteinuria of more than 3.5 g/day.
2. Hypoproteinemia: Serum total protein below 6.0 g/100 ml (or hypoalbuminemia of below 3.0 g albumin/100 ml serum).
3. Hyperlipemia: Serum total cholesterol in excess of 250 mg/100 ml.
4. Edema

Notes: 1) Proteinuria and hypoproteinemia (or hypoalbuminemia) are essential for the diagnosis.
2) Hyperlipemia and edema are not necessary for the diagnosis.
3) The presence of numerous oval fat bodies or doubly refractile fat bodies in urinary sediment is of diagnostic reference, though not definitive.

(II) Nephrotic syndrome in childhood
1. Proteinuria: Persistent proteinuria of above 3.5 g/day or 0.1 g/kg/day, or above 300 mg/100 ml of urine collected first in the morning.
2. Hypoproteinemia:
   - Total protein: children of school age below 6.0 g/100 ml; low-aged children, infants below 5.5 g/100 ml
   - Albumin: children of school age, infants below 3.0 g/100 ml; low-aged children below 2.5 g/100 ml
3. Hyperlipemia:
   - Serum total cholesterol: children of school age above 250 mg/100 ml; low-aged children above 220 mg/100 ml; infants above 200 mg/100 ml
4. Edema

Notes: 1) Proteinuria and hypoproteinemia are essential for the diagnosis.
2) Hyperlipemia and edema are of diagnostic help, though not providing definitive evidence.
3) Persistent proteinuria signifies a proteinuria lasting for 3 to 5 consecutive days.

Different territories were compared in such areas as Aomori Prefecture in northern Japan and Fukuoka Prefecture in the south as well as Tokyo on the mid-Pacific coast and Niigata Prefecture bordering the middle coast line of the Japan Sea, and each was found to be substantially the same. It may thus be stated that nephrotic syndrome occurs at a nearly uniform rate throughout the country.¹

The peak frequency of age at onset was found between 5 and 9 years old (mainly around 6) and then again in the early half of the twenties. Thereafter, the incidence declined with advancing age. That is to say, the age-frequency curve for nephrotic syndrome has two peaks, one in childhood and the other in the first half of the third decade.¹ These findings indicate that the nephrotic syndrome in Japan is also among those diseases which tend to affect young populations. It seems that the relative frequency of the syndrome in juveniles and young adults is explained largely by the fact that in the majority the glomerulonephritis is responsible for this syndrome (Fig. 1).

Difference in the incidence between sexes:

During childhood the incidence of the nephrotic syndrome is overwhelmingly higher
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Fig. 1. Sex ratio, age distribution and incidence in primary nephrotic syndrome

in boys than girls. Boys less than 5 years old are susceptible to this syndrome 5 times more than girls of corresponding age; at an age of 5 to 9 years boys are 3 times more frequently affected than girls. However, at the age levels of 15 to 19 years the male-to-female ratio diminished to 1:6 showing a slight predominance of male over female. Those aged between 20 and 50 showed little difference between sexes, the male-to-female ratio approximating to 1:1. It may be stated, therefore, that the incidence status at an age level of 15 to 19 years is intermediate between those of children and adults. The sex difference becomes noticeable again at age levels of above 50, with a slight predominance of males being observed. On an overall age basis males are affected by the nephrotic syndrome about twice as frequently as females (Fig. 1).

Since it is obvious that these data concerning the age at onset and the sex distribution of patients are closely related to the fact that the nephrotic syndrome is etiologically of either primary or secondary renal disease origin, it is considered necessary to further investigate these fundamental renal diseases, which would certainly contribute to a clarification of the clinical entity in question and to its successful management.

**DRUG THERAPY**

There are a number of problems yet to be solved in the treatment of nephrotic syndrome at present. Steroids, a major remedy for this syndrome, prove to be effective in most of the primary nephrotic syndrome and those secondary to SLE. However, not a few cases have frequent relapses while on steroids or prove unresponsive to steroid therapy. In order to find a solution to those problems, the two study groups mentioned elsewhere have come to some agreement, including the following two itemized matters.

1) Standardized criteria for evaluation of the renal biopsy findings are to be set up to ensure a proper, unbiassed reading of the renal histological features. And by using such criteria, a study is made to correlate the renal histological changes and drug effects.

2) The effects of drug therapy are to be evaluated in terms of the short-term (6-month) effect and the long-term (both 2-year and 5-year) effect.

From such a viewpoint, retrospective studies are now being made not only with steroids but also with other drugs. These studies are expected to contribute to the
proper evaluation of drug therapy, as well as further the proper decision on a therapeutic program, including the evaluation of prognosis and the elucidation of the pathogenesis of nephrotic syndrome.

The study results of the Research Council for the Treatment of Adult Nephrotic Syndrome in Japan regarding the effects of steroid therapy on clinical features and prognosis are briefly summarized next.2)

Improvements of clinical features:

Fig. 2 illustrates the time course of changes in proteinuria, serum total protein and serum cholesterol under steroid therapy in 216 steroid-responsive cases. As can be seen, a decrease in proteinuria was the first to be observed, followed by an elevation of serum total protein and then by a lowering of serum cholesterol. Return to normal values of these laboratory data occurred in the same order, but a more extended time period was required before it was accomplished. It should be noted that there was a close correlation observed between the degree of symptomatic improvement and the total dose of steroid.

Prognosis:

A study of 213 cases which were followed up for 5 years subsequent to initial steroid therapy as to the short-term (6-month) vs. long-term effect of the therapy showed that there were 149 cases (69.9%) in whom steroid therapy proved to be effective at 5 years. A further review of 154 cases whose therapeutic outcome could be evaluated after at 2 and 5 years revealed that a little more than half of the series (54.4%) benefited from steroid after 2 years of therapy, and further 115 cases (74.6%) were considered as benefited by the 5-year use of the drug.

In the statistical study of the long-term prognosis of nephrotic syndrome, Furukawa3) analysed pertinent data accumulated by the Research Council for the Treatment of Adult Nephrotic Syndrome in Japan using statistical analysis of the Markovian process. For purpose of this study he classified the patients' state into 5 categories, i.e. complete remission (with no demonstrable proteinuria), incomplete remission I (proteinuria less than 1 g/day), incomplete remission II (proteinuria more than 1 g/day), worsening and death. According to the author, the percentage of cases with complete remission reduced to 45%
after 3 years. In other words, 55% of cases had a relapse in the course of 3 years and this figure is in good agreement with relapse rate of more than 50% occurring within 5 years of initiating steroid therapy obtained from a relapse study. Of cases with complete remission, 15% died in the succeeding 5 years and 35% in 10 years.

Only about 30% of those cases classified as incomplete remission I remained in this state in the subsequent 5 years. This means that some change occurred in the patient's state during this time course in the remaining 70% of the cases. Of this group of patients, approximately 35% are supposed to have shifted to a state of complete remission. In the group of incomplete remission I, 8% had a fatal outcome in 5 years and 23% died in 10 years. Incomplete remission II accounted for 20% of the total cases at 3 years and 15% at 5 years. Of 85% of cases where there was a change to an other state, 30% were accounted for by a change to complete remission. Death from incomplete remission II occurred in 5 years in 14% and in 10 years in 30%. The percentage of nonresponders to steroid reduces to 20% in the course of 5 years. Of 80% showing a change to another state, approximately 10% changed to complete remission during this time course; 10%, 55% and 72%, respectively, died in 1, 5 and 10 years. The prognosis of those cases classified as worsening was generally very poor, with a mortality of 55% and 100% in 1 and 4 years respectively.

At 5 years after initiating the steroid therapy, 35% of cases with incomplete remission I, 30% of those with incomplete remission II and 10% of nonresponders were found to be in a state of complete remission. These findings are considered important in the evaluation of the prognosis for the nephrotic syndrome and also to serve as a guide for successful drug therapy.

Some of the above data investigated by using the Markovian process concerning the prognosis of nephrotic syndrome appear to be somewhat contradictory to actual clinical experience, however from the viewpoint of long-term prognosis, as Furukawa pointed out, it seems that there is no major distinction between complete remission and incomplete remission I.

Relapse:

Relapse is one of the most and vital problems in the management of nephrotic syndrome. We arbitrarily classify the changes of clinical symptomatology roughly into three categories, i.e. relapse, exacerbation and worsening. The following description will be limited to the relapse problem.

A 5-year follow-up study on relapse of the nephrotic syndrome under steroid therapy showed that of 103 cases where the short term result was classified as complete remission, 32 (31.3%) exhibited relapse and 29 others (28.8%) did not show any alterations in symptomatology in the interim. The ratio of the relapse group to the non-relapse group thus approximated to 1:1, and this implies that the relapse rate might well exceed 50%. These results were in good agreement with Furukawa's data obtained by using the Marcovian process and at the same time suggest the importance of a close analysis of relapse cases under the steroid therapy.
Histological findings and drug effects:

It is an incontestable fact that there is a fairly good correlation between the renal biopsy findings and the effect of steroid therapy. According to the results of a 5-year follow-up study of 128 cases conducted by the Research Council for the Treatment of Adult Nephrotic Syndrome in Japan, the minimal changes group was most responsive to steroids, followed by the proliferative group. In the membranous group, a smaller proportion of cases responded to the therapy, while in the sclerosing group, complete remission was not achieved in any one of the cases.²,³

Sakai and co-workers⁵ of our department classified their series of 165 cases of primary nephrotic syndrome into the following groups according to the renal biopsy findings.

(1) Minimal changes group ................................................................. 73
    without focal glomerular sclerosis ........................................ 61
    with focal glomerular sclerosis .............................................. 12

(2) Proliferative glomerulonephritis ........................................... 58
    pure proliferative.............................................................. 42
    advanced chronic ......................................................... 6
    membrano-proliferative ................................................... 10

(3) Membranous glomerulonephritis ........................................... 34

When the effect of steroid therapy was studied in relation to the histological varieties defined above, it became obvious that the minimal changes group generally responded well to steroids, but the group with focal glomerular sclerosis gave no consistent results, steroid therapy proving to be effective in some cases while ineffective in others. A distinct tendency to relapse in cases with minimal changes was recognized to be associated frequently with the presence of focal glomerular sclerosis. Although there are reports stating that the presence of focal glomerular sclerosis is associated with rather unfavorable prognosis, our impression is that the prognosis for such cases is not so poor.

Proliferative glomerulonephritis may be divided into a few subtypes according to the qualitative differences of proliferative changes. These qualitative differences may have repercussions on response to steroids. Thus, whereas cases with mild proliferative changes in glomeruli are responsive to steroids, those with advanced sclerotic changes are poorly responsive.

In the cases of membrano-proliferative glomerulonephritis, subendothelial deposits most commonly predominated electron microscopic findings and dense intramembranous deposits as described by Habib⁶ were very rarely seen. In this group of cases, steroid therapy proved to be invariably ineffective.

The incidence of membranous glomerulonephritis is significantly higher than a corresponding figure reported previously by Cameron⁹. The study further indicates that in this variety, steroid therapy was effective in 60% of cases and ineffective in 40%. During a follow-up period of up to 11 years, only 2 of 34 cases developed renal insufficiency, 5 others remained in a complete remission, another 12 continued to show the incomplete
remission I and the remainder were unchanged. From these results, which are similar to those reported by Pollak et al., it would seem that membranous glomerulonephritis runs a far more chronic course than was formerly believed.

Therapy resistant cases:

Besides steroids, immuno-suppressive drugs, non-steroid anti-inflammatory agents and anticoagulants are available for the treatment of nephrotic syndrome. At the present time steroids are the drug of first choice for primary nephrotic syndrome. In steroid-resistant cases, azathiopurine and cyclophosphamide are used, but these drugs are aimed primarily at inhibiting relapse in cases with a distinct tendency to relapse. Our experience shows that approximately one-third of nonresponders to steroid apparently have benefited from the subsequent use of immunosuppressants. Anticoagulants, such as dipyridamole and heparin are also found useful in cases of rapidly progressing nephrotic syndrome, where it may result in arrest of disease progression and recovery of renal function in some occasional cases. There also are cases where orally administered dipyridamole brings about a decrease in or even disappearance of proteinuria.

Steroid therapy used alone or in combination with immunosuppressants may prove to be of no value. Such a failure with steroids accounted for 20% of 204 cases. It is considered an urgent necessity to clarify the reasons for such therapeutic failures.

Our collaborators Ishimoto and others recognized a marked increase in urinary excretion of low molecular weight proteins (β2-microglobulin) and complement components (βC/βA globulin and βE globulin), in cases where steroid therapy proved unsuccessful. In contrast, steroid-responsive cases showed little or mild increase in urinary excretion of such low molecular proteins. These facts warrant us to infer that urinary tubules are extensively involved in refractory cases. However, this does not, of course, provide ample explanation for the observed failure with steroid. Further studies are indicated in order to clarify these uncertainties. The above data might provide us with a clue to the prediction of drug effect.

In conclusion, what has been stated so far is a part of the current status of research activities for the nephrotic syndrome of Japan. An extensive work on a nation-wide scale as lead by these two groups has been under way with a some productive results including the one described above. These results, however, are mostly dealt with the primary nephrotic syndrome and as yet the secondary nephrotic syndrome leaves much to be clarified.

Clinical manifestations of the nephrotic syndrome mainly stem from massive proteinuria. In a sense the true picture of this syndrome is not to be exposed without elucidation of the control mechanism of protein excretion, particularly of albumin. It is so expected that the mechanism be better understood in the near future.

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