Prognostic Implications of Certain Kidney Function Tests in Diffuse Glomerulonephritis

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The severity of diffuse glomerulonephritis may be evaluated by the data of various kidney function tests in reference to other clinical data, and prospective estimation on the prognosis of the patient might be made. Although a variety of complicated factors makes it difficult, informations from the renal functional status might provide an essential clue for evaluating the prognosis of the patient. However, seldom investigations have provided an information on prognostic implications of function tests, or the prognostic features of the patient based on a severity figure of the renal function. In this study, an investigation was made to evaluate the prognostic implications of practically used function tests in a series of unselected consecutive hospitalized patients with diffuse glomerulonephritis. The survival patterns of the patients were analysed based on the substantial initial severities of function tests at the admission, such as Fishberg’s concentration test, PSP test, serum NPN level, glomerular filtration rate, and renal blood flow.

The prognosis of diffuse glomerulonephritis is variable; some patients remain in good health for years, while others develop disabling or fatal outcome. This also is the case in primary hypertension. However, prognostic estimations based on a severity figure of disease have been less sufficiently made in patients with glomerulonephritis than in those with primary hypertension. Although a number of excellent articles described natural history of diffuse glomerulonephritis,1)-11) seldom investigations have been made on the prognostic evaluation concerning the renal functional status.

Various kidney function tests provide an essential clue for evaluating the degree of the functional impairment resulting from the glomerular
lesion, and the severity of the disease may be assayed from this clue in reference to other clinical data. As a matter of course, the renal functional status is a problem of vital importance among various features indicating the severity of the disease. Then, changes observed in kidney function tests might be an essential factor indicative of the prognosis, and considerations on the problem of prognostic implications of certain kidney function tests would be of most significance for the prospective estimation on prognosis of the patient. It is of practical importance to investigate whether certain severity in individual function test does provide the clues which enable the physician to predict the course in a particular patient, and that, if does so, in what degree. This information is also necessary in order to evaluate the effects of other drug or management in the future, such as consecutive ambulatory treatment by artificial kidney for example, in prolonging life in patients with chronic glomerulonephritis.

On the bases of considerations discussed above, the present study was undertaken to evaluate the prognostic implications of practically used 5 kidney function tests in a group of unselected consecutive patients with diffuse glomerulonephritis.

**Material and Method**

Two hundred and twenty-three protocols with diagnosis of diffuse glomerulonephritis were selected consecutively from the hospital records registered during the last 10 years up to January 1961, at the 2nd Department of Internal Medicine, Tokyo University Hospital. The actual number of patients in these protocols was 212. Fatality was investigated into these 212 patients in September 1961. Forty-three of them had died in our hospital and 20 had been under the observation in our clinic at that time; accordingly, personal correspondence was firstly made for another group and finally, inquiry for the census registration offices was made in order to trace the remainders. Consequently, 201 (95%) of 212 patients could be traced and 11 (5%) were lost. These 201 patients (total number of admissions 212) served for this study. They consisted of 169 cases with chronic glomerulonephritis including 25 cases with nephrotic syndrome (6 cases of subacute form included), and 32 cases with acute glomerulonephritis including 8 cases of residual albuminuria. None of the so-called true nephrosis was involved. Most of all cases with acute nephritis were admitted to the hospital after the culminating phase. Thirty-two cases were autopsied, and kidney biopsy study was made in 40 cases in the latest 3 years. There were 125 males and 76 females. The age ranged from 13 to 73 years with an average of 33.8 years. The observation period which means from the time of registered individual kidney function test to the follow-up time ranged from 8 to 129 months, with an average of 57 months. Numbers in total of the patients of their observation period of more than 3, 5 and 10 years were 133,
87, and 7 cases respectively.

From the various kidney function tests determined in the subjects, Fishberg’s urine concentration test, phenolsulphonphthalein (PSP) test, serum non-protein-nitrogen (NPN) level, glomerular filtration rate (GFR), and renal blood flow (RBF) were selected for evaluating their prognostic significance of clinical use in patients with glomerulonephritis. Though determinations of these tests were usually performed 2 or more times during the hospital course, only the initial value of each test in an individual admission was served for analysis except in a few patients of serving the 2nd value, in whom the initial determination was made at a labile state, for instance, transient heart failure. Fishberg’s concentration test, PSP test and NPN level were determined by routine procedure; GFR and RBF were calculated from the simultaneous determinations of endogenous creatinine (in the majority of the cases) and injected p-aminohippurate (in 1/4 cases by standard method and 3/4 by single injection method) in the serum and urine which washed-out through a urethral catheter during about 20 to 30 minutes’ clearance time.

The materials of 5 groups with these kidney function tests were divided into subgroups according to the severity of each test, and the yearly or monthly cumulative survivals were determined by the statistical method of Hill, and were illustrated up to the 5th year.

**Results**

In actual 201 patients, 73 (36%) deaths (58 in males and 15 in females) were observed during a variety of periods of time (number of deaths in total was 79 among 212 of total cases). All deaths except 1 were found in patients of chronic glomerulonephritis. Forty-three patients died due to uremia in their hospital course, 12 of other 30 cases died of uremia or of related conditions and 1 of a traffic accident after the discharge, and in the remaining 17 cases the cause of death could not be confirmed.

*Concentration test:* Concentration test was performed in 136 of total 212 cases. There were 42 deaths in total. Number of the cases and deaths, divided into 5 severity grades, are listed in Table I. Fig. 1

<table>
<thead>
<tr>
<th>Maximum specific gravity</th>
<th>No. of cases</th>
<th>No. of deaths (%)</th>
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<tbody>
<tr>
<td>≥ 1.031</td>
<td>36</td>
<td>5 (14)</td>
</tr>
<tr>
<td>1.030–1.026</td>
<td>18</td>
<td>2 (14)</td>
</tr>
<tr>
<td>1.025–1.021</td>
<td>28</td>
<td>6 (21)</td>
</tr>
<tr>
<td>1.020–1.016</td>
<td>22</td>
<td>8 (36)</td>
</tr>
<tr>
<td>≤ 1.015</td>
<td>32</td>
<td>21 (64)</td>
</tr>
<tr>
<td>Total</td>
<td>136</td>
<td>42 (31)</td>
</tr>
</tbody>
</table>
indicates the yearly cumulative survivals in these 5 subgroups. The curves were arranged into about 3 groupings, namely, 3 subgroups of more than 1.020, subgroups of 1.020–1.016 and of 1.015 or less. In the most severe subgroup, the probability of surviving at each year was calculated as 47%, 40%, and 30% respectively. In the subgroup of 1.020–1.016, it was 77%, 65%, and 59%, indicating distinctly higher survival than that of 1.015 or less. The group of highest survival rate consisted of 3 subgroups among which no difference was found up to the 3 year survival, though the 4 year's rate of the subgroup of 1.025–1.021 was apart from the others. A good survival responsibility on the initial value of concentration test was found among 3 severity gradings, viz. more than 1.020, 1.020–1.016, and 1.015 or less.

**PSP test**: Seventy cases had PSP determination and 26 (37%) of them died. According to the degree of the dye excretion of 15 min. the cases were divided into 3 subgroups. The results are listed in Table II. As shown in Fig. 2, the survival pattern revealed higher rates in 2 subgroups of more than 10% and remarkably low rate in the subgroup of less than 10%. In the most severe subgroup, 16 of 19 deaths were observed.

<table>
<thead>
<tr>
<th>Per cent excretion</th>
<th>No. of cases</th>
<th>No. of deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 25</td>
<td>26</td>
<td>2 (8)</td>
</tr>
<tr>
<td>10–24</td>
<td>20</td>
<td>5 (25)</td>
</tr>
<tr>
<td>≤ 9</td>
<td>24</td>
<td>19 (79)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>70</strong></td>
<td><strong>26 (37)</strong></td>
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in the 1st year, and remaining 2 and 1 in the 2nd and 3rd year, indicating each year survival rate of 33%, 21% and 0% respectively. However, no validity should be given on the last feature of the survival rate because there was only 1 patient exposed to risk during the 3rd year in this subgroup. Similarly, in the subgroups of 25 or more and of 10-24%, 1 and 4 cases were exposed to risk on the latest segments of the curves. Despite a decreasing reliability of the results due to short duration of observation period and relatively small number of subjects, it was indicated that the survival difference between the subgroup of less than 10% and others may be of significance.

**NPN level**: Available serum NPN determination at the admission was found in all but 6 cases. The degree of the NPN level was classified as normal (≤ 29 mg./100 ml.), borderline (30-39 mg./100 ml.), or azotemia (≥ 40 mg./100 ml.). Azotemia was subdivided further into 4 degrees: 40-79, 80-119, 120-159 and 160 mg./100 ml. or more. The numbers of the subjects and deaths in each severity are shown in Table III. Fig. 3 illustrates the cumulative survivals which were calculated

<table>
<thead>
<tr>
<th>Serum NPN level (mg./100 ml.)</th>
<th>No. of cases</th>
<th>No. of deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 29</td>
<td>72</td>
<td>8 (11)</td>
</tr>
<tr>
<td>30-39</td>
<td>46</td>
<td>10 (22)</td>
</tr>
<tr>
<td>40-79</td>
<td>49</td>
<td>23 (47)</td>
</tr>
<tr>
<td>80-119</td>
<td>20</td>
<td>17 (83)</td>
</tr>
<tr>
<td>120-159</td>
<td>7</td>
<td>7 (100)</td>
</tr>
<tr>
<td>≥ 160</td>
<td>12</td>
<td>12 (100)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>206</strong></td>
<td><strong>77 (37)</strong></td>
</tr>
</tbody>
</table>
on 5 subgroups, viz., normal, borderline, slight azotemia (40–79 mg./100 ml.), moderate azotemia (80–119 mg./100 ml.), and marked azotemia (≥ 120 mg./100 ml.). At sight, 2 distinctly different features were found between the subgroups of moderate or marked azotemia and others. In the formers, the prognosis was so catastrophic as to calculate the survivals monthly. In marked azotemia, 8 deaths occurred in each of the 1st and 2nd month, and remaining 3 cases succumbed up to the end of the 7th month. The probability of surviving at the ends of the 1st, 2nd and 6th month was indicated as 58%, 16% and 6%, respectively. The average duration of life was calculated as 1.6 months in these 19 cases with marked azotemia (2.2 months in 7 cases with NPN level of 120–159 mg./100 ml., 1.2 months in 12 of 160 mg./100 ml. or more). In moderate azotemia, 12 of 20 cases died at the end of 6th month and other 5 cases died up to the end of the 2nd year, indicating the survival rate of 40% and 10% at respective time. The longest observation period in a living case was 26 months. In the subgroup of slight azotemia (40–79 mg./100 ml.), the probability of surviving was strikingly increasing than that of the formers. Survival rate at each year was calculated as 77%, 71%, 60%, 52%, etc. On the other hand, high survival rate (about 85% in 3 years) was shown in the subgroups of “borderline” and “normal”, indicating no distinct difference between them. In this group, the value of more than 80 mg./100 ml. of the initial NPN level revealed a strikingly decreased probability of surviving, whereas the rate progressively decreased as the value increased 40 mg./100 ml.
Glomerular filtration rate: Table IV represents the survey of 195 subjects in which glomerular filtration rate was determined. As shown in the table, every 20 ml/min. range was given to classify the severity of the initial GFR. Forty-three (84%) deaths were observed in 51 cases of most severe subgroup (≤ 19 ml/min.), and fatality was decreased in the less severe subgroups with increasing every 20 ml/min. of GFR. As shown by the curves graphed in Fig. 4, yearly cumulative survival rates were proportionally distributed among 5 severity grades. In the subgroup of less than 20 ml/min. of the initial GFR, 38 deaths were observed in the 1st year, 2 and 1 deaths in the succeeding years; indicating each year survival rate of 25%, 21% and 18%. The 3rd year survival rate in the subgroups of 20–39, 40–59, 60–79 and 80 ml/min. or more was calculated as 42%, 72%, 88% and 98%, respectively. In GFR group, survival difference was found among over all 5 severities, for which every 20 ml/min. range of GFR was used as a severity grading. The relationship was correlative.
Renal blood flow: All patients except 1 in RBF group were identical with those in the group of GFR. One dead case of GFR group had not RBF, and another living case had only RBF determination. Thus, there were 72 deaths among 195 subjects. Grading of the severity was made by every 200 ml/min. range of RBF. The results are tabulated and illustrated in Table V and Fig. 5. As indicated by Table V, an increasing per cent mortality was seen as the severity gradings increased, suggesting a good relationship of prognosis and severity in the initial RBF, however, as illustrated by the survival pattern in Fig. 5, it was not so good as found in GFR group. The survival difference up to the 5th year between 2 subgroups of normal (≥800) and subnormal (600–799) was almost negligible, and between more severe succeeding 2 subgroups it was less apparent than that in GFR group. The survival curve in the most severe subgroup, indicating somewhat lower figure than that of corresponding subgroup in GFR,
revealed remarkable separation from others. The survival rate at the end of 3rd year in respective severity was indicated as 97%, 91%, 72%, 62% and 11%.

Discussion

Significance of an impaired kidney function in patients with diffuse glomerulonephritis varies according to their course of the disease. Of special reference is the difference between acute nephritis or exacerbation in chronic phase and established chronic nephritis; for whereas once renal function has been impaired in the latter it does not improve as a rule, in the formers all or any of impaired function which may reach to extreme degree may return toward the preceding level within several weeks or months as improvement of the acute process. It should be taken into discussion at first that; despite a minority of the cases, groups of 24 cases (12% in total material) of acute glomerulonephritis and of some other cases which might be in acute exacerbation were included in the material, even though the most of cases with acute type admitted to the hospital after the culminating phase. An allowance would be given for this because of the followings: the purpose in the present study was to evaluate on the prognostic implications of kidney function tests in a clinical use, irrespective of other factors including signs or symptoms; and an analysis was made for this on the initial values of the tests, except a few cases, in a series of unselected hospitalized patients.

By means of the follow-up study, 95% (201 cases) in original series could be traced with a result of 73 fatal cases developing for an observation period of averaging about 5 years, however, unfortunately, the cause of death could not be clarified in 17 cases. A minor probability of death developing unrelated with nephritis might be expected in these 17 deaths of non-proved cause, as referred to only 1 death of traffic accident in 56 deaths of proved cause. Nevertheless, it seemed reasonable that rather to include these fatal cases of which cause of death was undetermined or unrelated with nephritis than to exclude as a material in this study.

The main features of the results in this survey indicated that, in general, the probability of survival in patients was to be decreasing as a severity increased in the kidney function tests, however, there were considerable differences among them.

Concentration test, a most simple procedure, has been widely used into practice. Fishberg\(^9\) described that, up to the point of isosthenuria, the specific gravity is believed to be the most useful index for following the progress of renal damage. Recent investigations from
various approaches\textsuperscript{13)-18)} have brought a revolution into the previous concept on the concentrating power of the kidney, and evidence has strongly suggested that diminished concentrating power in diseased kidney is due to osmolar diuresis resulting from an overload on decreased intact nephron.\textsuperscript{17),18) Though this may not always be applied in all the cases,\textsuperscript{19)} as a matter of fact, there is no direct relationship between specific gravity and osmolarity for which concentrating power is responsible, unless the urine contains solutes in a constant composition. Moreover, some other factors make the result precarious. In this study, survival pattern in 5 proportional severity gradings revealed not so good relationship of survival and severity unless maximum specific gravity decreases below 1.020, suggesting some limitations of this test as an aid of prognostic estimations. However, it is of practical importance that survival difference was found among 3 gradings, viz. more than 1.020, 1.020-1.016 and 1.015 or less.

The long established PSP excretion test has been utilized as quantitative evaluation of renal function. About 6 per cent of the total dye excreted is eliminated by filtration and 94 per cent by tubular activity.\textsuperscript{20) For the evaluation of the test, excretion rate of 15 min. collection period has been recommended as an available datum, because the kidneys are given the opportunity repeatedly to clear the blood of PSP, and a normal value for total 2 hour excretion may be obtained despite a functional impairment. The survival pattern in the group of PSP test suggested that the prognosis is markedly deteriorated when the value decreases below 10%. No proportional decrease in survivals was found among roughly divided 3 severity gradings in the survey, suggesting a little prognostic implications among the values of more than 10%, however, further studies are advisable to determine the conclusive features of this test.

It has been well recognized that marked elevation in serum NPN level gives a grave sign to the prognosis of patients with chronically diseased kidney. In advanced renal failure, serum NPN level is most useful as an index for following the progress of further deterioration. Clinical experiences teach us that once renal decompensation with azotemia appears in chronic renal disease, only a minority of the patients survive more than a few years; and impressions are occasionally gained that the worse prognosis may be expected in the more severe azotemia in spite of the facts that the tempo with which the disease reaches its fatal termination varies markedly from case to case and it may be largely influenced by the treatments on diet and body fluid. However, impressions are to be claimed by the lack of analytical data. In this study, survival pattern in the group of NPN revealed remarkable difference between slight azotemia (40-79 mg./100 ml.) and moderate azotemia (80-119 mg./
The survival curves in 2 subgroups of 80–119 and 120 or more showed abrupt decrease to approximately 20% at 8 and 2 months respectively, indicating discernible difference between both gradings. On the contrary, in slight azotemia, probability of survival was expected to be about 80% at 1 year and 50% at 3 years. Slight azotemia indicated considerable difference from the group of normal and subnormal, of which value may be accidentally obtained resulting from environmental factors such as diet, dehydration, or concealed circulatory insufficiency, etc. The review of the recent literature hardly found the analytical study of prognostic evaluations regarding the NPN level in diffuse glomerulonephritis. In the survey of Asano and others,21) in followed-up 60 cases with chronic glomerulonephritis, it revealed that all 18 cases with NPN of more than 120 mg./100 ml. died within 6 months and in a group of more than 40 mg./100 ml. there were 46 deaths observed within 2 years among 49 cases. In the present study, it is of practical importance that the prognostic implications of available initial NPN values were analysed.

The development of clearance methods by H. Smith’s school brought a brilliant advancement into the functional evaluation of the diseased kidney. Precise determinations have been able to be made in the kidneys on glomerular filtration rate and renal blood flow, by means of the sustained infusions of GFR substances and p-aminohippurate. While these methods supply a wealth of accurate informations about renal function, they are too complicated to be of clinical benefit. Of much benefit to the clinician are such tests as endogenous creatinine and injected PAH clearances. The endogenous creatinine clearance would afford a measure of glomerular filtration rate,22)-26) being closely comparable (except in the lowest values and normal range) with inulin clearance which should closely approximate the true glomerular filtration rate. The PAH clearance by single injection method,27),28) by which about 3/4 subjects were determined, is to be of clinical measure of renal plasma flow in numbers of patients, even though it may have little discrepancy as compared with the standard method. In actuality, endogenous creatinine and injected PAH clearances have so slight differences from the true values of GFR and RPF as to possess little clinical significance. They have been utilized in practice as measures of precise renal functions, however, the detailed prognostic significance in them has remained to be answered. Effer29) demonstrated the survival curve for the selected 37 patients of chronic renal disease with the clearances of urea or endogenous creatinine (24-hour) below 20% of the normal value. In Asano’s report,21) 42 deaths out of 43 cases with endogenous creatinine clearance below 30 ml./min. were found during 2 years, indicating lower incidence of survival than ours. Tobias et al.26) described the endogenous creatinine clearance
as a valuable prognostic guide in chronic renal disease, based on a survey of total cases in which only 3 survivors for 4 years were found out of 21 patients with 30 ml./min. or below. In the present study, it must be emphasized that correlative relationship was demonstrated between prognosis and GFR severities for which every 20 ml./min. range was used as a grading.* Moreover, in comparison with RBF, difference of survival pattern between them is noteworthy. The observations indicated that; corresponding deteriorations in prognosis of the patients may be evaluated by the degree of decreasing GFR values below the normal range; the values of the initial RBF have to be given some limitations as an index to prognosticate the patients of diffuse glomerulonephritis. The inferiority of RBF as compared with GFR may be responsible for the characteristic of the disease—glomerulonephritis as a primary disease of glomerular lesion. Evidence observed in patients with primary hypertension, indicating superiority of RBF, supports this view.

General impressions may have been held that a single set of renal function tests provide a little informations concerning the prospective estimations on prognosis in particular patients, except in the terminal stage. These are mainly due to the variations in the course of the disease, and moreover attendant difficulties in predicting the rate of progression. Of course degree of the reliability of the tests may be responsible. However, as shown in the results of this study, prognostic contributions might be found in the available data of a single set of function tests even in a simple one such as concentration test, though some limitations must be considered. Nowadays, the glomerular filtration rate, among a variety of tests of clinical benefit, is the most sensitive indicator of renal damage early in the course of diffuse glomerulonephritis. It is interesting to note that in this study the glomerular filtration rate was proved to be the most sensitive index as an aid of the prospective estimation of prognosis. As a matter of course, prognostic estimation in a particular patient is a problem of case by case, however, it must be emphasized that substantial data of function tests, even though a single set observations, provide the clues which enable the physician to predict the prognosis of the patients.

SUMMARY AND CONCLUSION

In 201 consecutive hospitalized patients with diffuse glomerulonephritis followed-up out of original series of 212 cases, the prognostic implications

* Supplemental analysis in which the relationship was examined among 4 severities divided by each 30 ml./min. range revealed the same result.
of practically used 5 kidney function tests were investigated. The average follow-up period of time was 57 months, ranging from 8 to 129 months. The number of deaths observed in this period was 73 (36%). Based on the substantial initial severity of the function tests at the admission, the materials in each group were divided into 3 to 6 subgroups, and cumulative survival rates up to the 5 years were illustrated. The results are summarized as follows:

**Fishberg's concentration test**: Among 3 severity gradings of maximum specific gravity of more than 1.020, survival difference was practically negligible. A good relationship of survival and severity was found among 3 gradings, viz. 1.021 or more, 1.020–1.016, and 1.015 or less, indicating 3 years' rate of approximately 90%, 60% and 30%, respectively.

**PSP test (15-min. excretion)**: In roughly divided 3 subgroups, remarkable survival difference was found between the most severe grading (less than 10%) and others. Considerable but a little difference was shown between 2 subgroups of 10–24% and 25% or more. Further study is advisable for this group.

**NPN level**: Remarkably different features were observed between 3 subgroups of serum NPN level of less than 80 mg./100 ml. and 2 subgroups of more. In the most severe subgroup (120 mg./100 ml. or more) survival rate reached nil at the end of 7 months with an average duration of life of 1.6 months, and in the subgroup of 80–119 mg./100 ml. survival rate decreased to 10% at 2 year, indicating considerable difference of both survivals. The survival rate at the end of 3 years in the subgroups of slight azotemia (40–79), borderline (30–39), and normal (30 or less) was 60%, 82% and 89%, respectively. Difference between the “borderline” and “normal” was almost negligible.

**GFR**: In the 5 severity gradings for which proportional GFR values by every 20 ml./min. range were given, a good relationship of survival and GFR severity was found. The relationship was correlative. The 3-year survival rate was indicated as 18% in the subgroup of 19 ml./min. or less, 42% in 20–39, 72% in 40–59, 87% in 60–79, and 98% in 80 or more, and the 5 years' rate in respective subgroups was 14%, 42%, 54%, 82% and 98%.

**RBF**: Decreasing survivals with increasing severity of RBF were not proportional among 5 subgroups for which grading every 200 ml./min. range was used. Negligible difference was found between the subgroup of 800 ml./min. or more and of 600–799, and difference between 400–599 and 200–399 was a little. As compared with GFR, reliability on prognostic estimation in this test was distinctly low.

The general conclusions which may be drawn from the data are:
1) available determinations of kidney function tests, even those of a single set observations, may provide more or less important prognostic informations; 2) contributions of the concentration test, PSP test, NPN level, and RBF have considerable limitations, however, they have individual characteristic features; 3) in the case of extreme renal failure, NPN level is most reliable; and GFR is the most sensitive prognostic index in the other case of diffuse glomerulonephritis.

References

30. Data to be published.