Differential Diagnosis of Chronic Kidney Disease (CKD): By primary diseases

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Abstract

In Japan, the number of patients with chronic kidney disease (CKD) is estimated to be approximately 13 million. Of these, the number of dialysis patients, signifying the terminal stage of CKD, reached 282,000 at the end of 2008. Every year, over 37,000 CKD patients enter dialysis therapy due to diabetic nephropathy, chronic glomerulonephritis, nephrosclerosis, polycystic kidney disease, or rapidly progressive glomerulonephritis (in descending order). Although the number of new dialysis patients due to chronic glomerulonephritis is on the decline, the number of new cases attributable to diabetes, hypertension, and arteriosclerosis is on the rise. In this paper, I present and seek the current status and problems related to CKD in Japan by examining the primary diseases.

Key words Chronic kidney disease (CKD), Diabetic nephropathy, Chronic glomerulonephritis, Nephrosclerosis, Drug-induced nephropathy

Introduction

Primary diseases of chronic kidney disease (CKD) can be determined by examining the primary diseases of the patients who eventually received dialysis treatment. According to a statistical survey conducted by the Japanese Society for Dialysis Therapy for Year 2008 (hereinafter referred to as the 2008 Survey), the total number of patients undergoing dialysis treatment is more than 282,000 as of December 31, 2008 (**Fig. 1**). As is clear from the graph, the number of dialysis patients has been increasing consistently year by year, with no sign of decline. There have been approximately 37,000 new dialysis patients every year. The most common primary diseases responsible for end-stage renal failure are; diabetic nephropathy, chronic glomerulonephritis, nephrosclerosis, polycystic kidney disease, and rapidly progressive glomerulonephritis (in descending order) (**Fig. 2**).

The 5 Top Primary Diseases in New Dialysis Patients in the 2008 Survey

According to the 2008 Survey, the 5 major primary diseases in new dialysis patients (excluding unknown cases) as of December 2008 (**Fig. 2**) are as follows:

1st: diabetic nephropathy (43.2%)
2nd: chronic glomerulonephritis (23.0%)
3rd: nephrosclerosis (10.5%)
4th: polycystic kidney disease (2.5%)
5th: rapidly progressive glomerulonephritis (1.2%)

Diabetic nephropathy has been ranked the highest since 1998 when it overtook the previous top, chronic glomerulonephritis, and gaining a good lead ever since. Considering the recent rapid increase in the prevalence of metabolic syndrome, the number of new dialysis patients due to diabetic nephropathy is likely to increase further, which calls for urgent efforts and measures from the viewpoint of CKD management. On the other hand, it is apparent that the number

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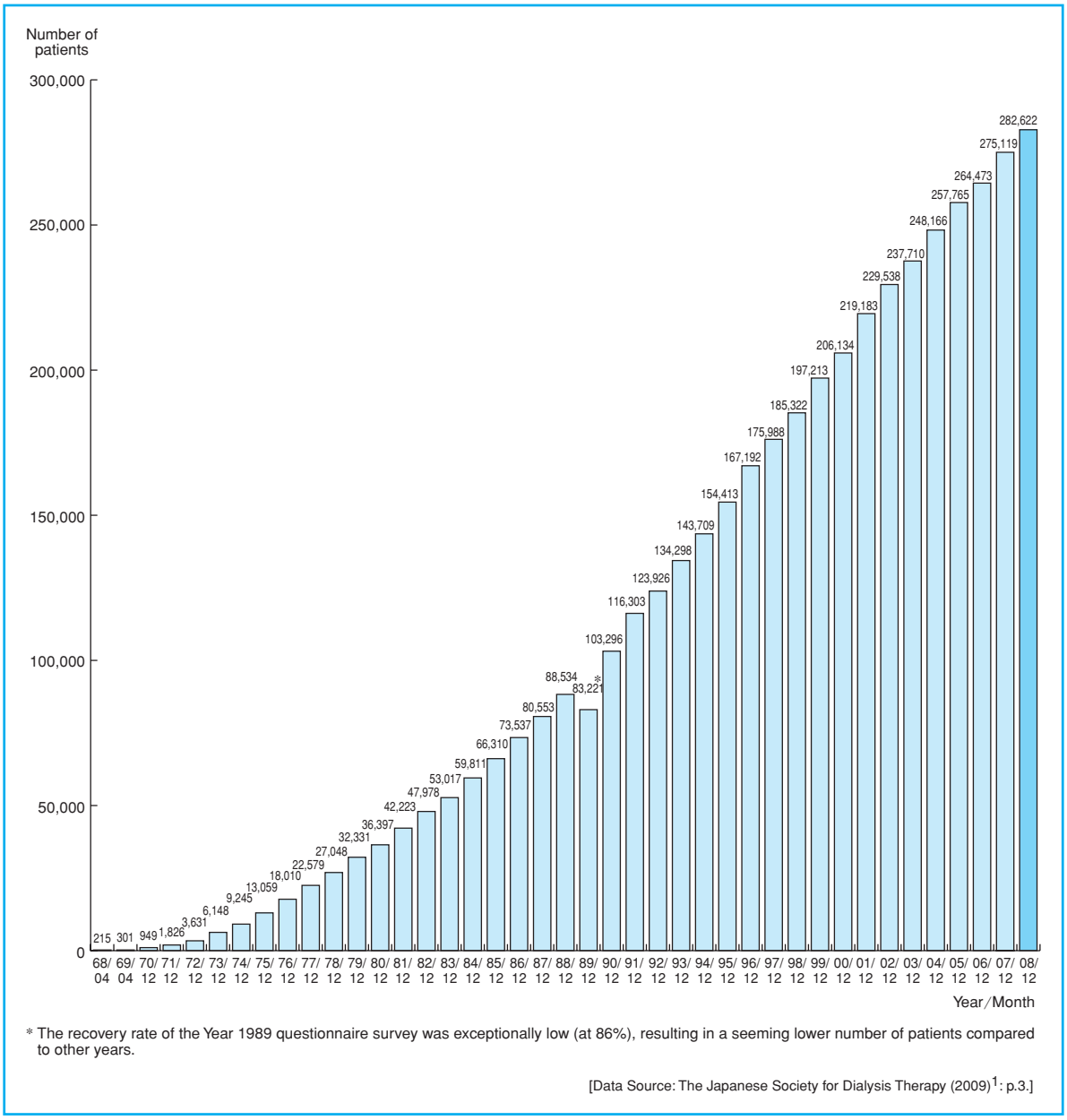

Fig. 1 Changes in the number of chronic dialysis patients

of patients with end-stage renal failure resulting from chronic glomerulonephritis has been decreasing gradually in recent years.

Various factors may be responsible for the decrease in dialysis patients due to chronic glomerulonephritis. One reason is that overall infections themselves, in which the occurrence of nephritis is involved, have been decreasing as public hygiene improves. This trend is said to be particularly obvious for acute glomerulonephritis and membranoproliferative glomerulonephritis. Another possible factor is that drug treatment for chronic glomerulonephritis has become more successful, including the result of so-called cocktail treatment that uses a combination of adrenocortical steroid therapy, antiplatelet therapy, and anticoagulant therapy. Furthermore, as a result of tonsillectomy and steroid pulse therapy, not

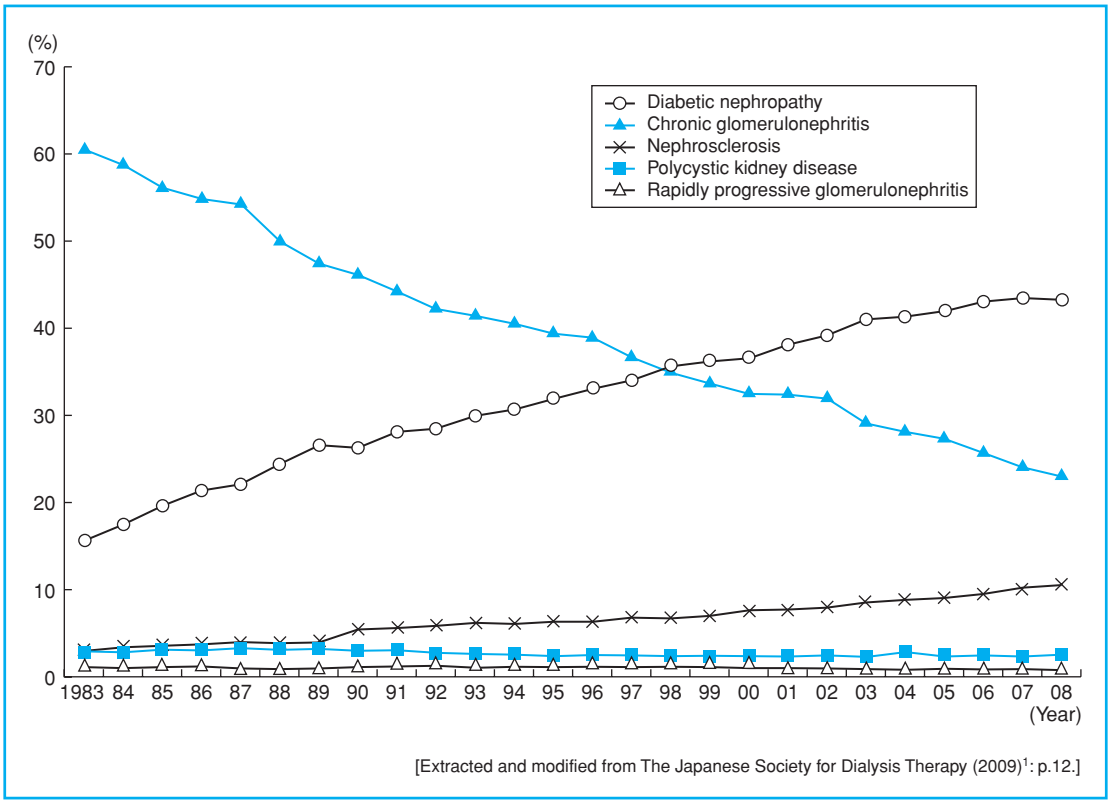

Fig. 2 Changes in the 5 major primary diseases in new dialysis patients by year

only remission but even cure has become possible in patients with IgA nephropathy who account for more than half of all patients with chronic glomerulonephritis.

Another aspect that should be noted strongly is the important role played by the annual school urinalysis screening (for children of age 5 to 15 in elementary and junior high schools in Japan). I shall forgo the details here, but it is apparent that school urinalysis has contributed to the early detection and treatment of nephritis. Therefore, it is recommended that urinalysis test be implemented in all employee health examination and complete physical examination for adults, in addition to elementary and junior high schools.

Nephrosclerosis, which is ranked the third, is expected to become more common in the future. In fact in the USA, nephrosclerosis overtook chronic glomerulonephritis and has taken the second place. Population aging is one contributing factor to the dominance of nephrosclerosis, of course; however, an increase in arteriosclerosis linked with metabolic syndrome is also in the background. Arteriosclerosis not only induces cerebrovascular or cardiovascular diseases but also increases renal disorders. This type of nephropathy, which is now being perceived as arteriosclerosis-related nephropathy, follows a rapid course and has a poor prognosis. To be specific, it exhibits various phenotypes, including malignant hypertension, renovascular hypertension, ischemic nephropathy, and cholesterol embolism.

The fourth-ranked polycystic kidney disease often exhibits an autosomal dominant pattern of inheritance. As shown in **Fig. 2**, the number of new dialysis patients resulting from this disease is almost the same every year. A new treatment method has been proposed, and the result is anxiously awaited.

Ranked the fifth is rapidly progressive glomerulonephritis, one of 5 clinical classifications of primary renal diseases prescribed by the World Health Organization (WHO). As implied by its name, deterioration of renal function

Table 1 Primary diseases in new dialysis patients in 2008

Primary disease	Total	(%)	Rank
Chronic glomerulonephritis	8,602	23.0	2
Chronic pyelonephritis	274	0.7	10
Rapidly progressive glomerulonephritis	443	1.2	7
Nephropathy of pregnancy/pregnancy toxemia	81	0.2	18
Other unclassifiable nephritis	158	0.4	14
Polycystic kidney disease	918	2.5	6
Nephrosclerosis	3,936	10.5	4
Malignant hypertension	282	0.8	9
Diabetic nephropathy	16,126	43.2	1
Systemic lupus erythematosus nephritis	285	0.8	8
Amyloidal kidney	187	0.5	13
Gouty kidney	100	0.3	16
Renal failure due to congenital abnormality of metabolism	18	0.0	22
Renal/urinary tract tuberculosis	22	0.1	21
Renal/urinary tract calculus	66	0.2	19
Renal/urinary tract tumor	188	0.5	12
Obstructive urinary tract disease	95	0.3	17
Myeloma	158	0.4	14
Renal hypoplasia	43	0.1	20
Post-transplant reintroduction	211	0.6	11
Other diseases	1,186	3.2	5
Cause unknown	3,976	10.6	3
Total	37,355	100.0	
No information available	124		
Grand total	37,479		

[Adapted from The Japanese Society for Dialysis Therapy (2009).[1]]

progresses rapidly over weeks or months. In most cases, extensive crescent formation is found in glomeruli, which also has been known to occur in cases of immune complex nephritis such as acute post-streptococcal glomerulonephritis, lupus nephritis, membranous nephropathy, membranoproliferative glomerulonephritis, and IgA nephropathy. In many cases, the crescent formation occupies more than 50% of glomeruli. In addition to these immune complex types, Goodpasture's syndrome, which is caused by the presence of an autologous antibody to the glomerular basement membrane, often involves rapidly progressive glomerulonephritis as well.

In recent years, relatively new pathological concept has been established; crescentic nephritis due to anti-neutrophil cytoplasmic antibodies (ANCA). Although case report of this disease is increasing in Japan, the details are yet to be investigated. Possible responsible factors include infections, drugs, air pollution, silica, and immunologic abnormalities. The characteristic of this disease is the presence of ANCA in the serum of the patients. The fact that public healthcare insurance of Japan covers the ANCA screening since 1998 may have brought the apparent increase in the number of cases. In other words, increasing knowledge of this disease by medical professionals and establishment of an easier means of diagnosis contributed to the recent increase. However, it cannot be denied that the actual number of patients is increasing together

with the rise of aged population and environmental changes. Considering that the patients occasionally reach end-stage renal failure before any chances of blood test or renal biopsy, some cases may have been classified as unknown cause.

Other Causes of CKD

Besides the 5 major primary diseases, many other diseases serve as causes of dialysis treatment (**Table 1**). Here, it should be noted that cases of unknown cause account for 10.6% at the third position. These cases presumably represent outpatients who were not followed regularly, who were unexpectedly admitted to hospital and eventually required dialysis treatment before any chance of proper examination—including many patients who have not sought treatment even though their abnormal urinalysis findings have been pointed out and those who progressed from acute renal failure. This indicates the importance of regular follow-up visits for outpatients. Due attention to avoid acute renal failure is also highly desirable since it is conceivable that drug-induced cases are particularly common. In any event, improvement in diagnostic capability is required.

Of the "other diseases" that accounts for 3.2% in **Table 1**, drug-induced nephropathy is likely the main cause. Drug-induced cases, if clearly identified, are included in this category, although unidentified cases would be classified as the unknown cause.

Major drugs responsible for drug-induced nephropathy are antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticancer drugs; however, the uric acid-lowering drug, allopurinol, is also of note. Allopurinol is frequently used in patients with CKD and potentially induces nephropathy. Although the Allopurinol dose should be reduced according to the deterioration of renal function, such close consideration is not often given in actual clinical practice. Clinically speaking, complication of acute interstitial nephritis due to allopurinol can bring about an acute-on-chronic renal failure, acting as a final push toward end-stage renal failure. The methods of diagnosis include the evaluation of clinical course, eosinophilia, presence of urinary eosinophils, increased urinary NAG, marked increase in urinary β_2 microglobulin, and increased renal uptake on gallium scintigraphy—all of which are not difficult. Close attention to these findings is required when administering allopurinol.

In addition, the increasing popularity of health awareness among the general public in recent years calls for cautions on the use of Chinese herbal medicines and supplements. Chinese herbal medicine is known to cause Aristolochic acid nephropathy, and the use of crude drugs such as Chinese moonseed *Sinomenium acutum* require particular attention. Aristolochic acid nephropathy takes the form of interstitial nephritis, lowering renal function with modest proteinuria. Among various supplements, vitamin D supplements require particular caution. Vitamin D is often prescribed for the treatment of osteoporosis; however, a dose of 1 μg may be too high in small framed elderly women, although this dose is covered by health insurance in Japan. Excessive intake of vitamin D often induces hypercalcemia, resulting in nephropathy. When the association is realized early enough, discontinuation of vitamin D improves the patient's condition. However, when the association is left unnoticed, patients may reach the stage of requiring dialysis.

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