



# On the Question of Neuroleptic Amyloidosis

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## Abstract

The article describes the observations of renal amyloidosis, developed in the course of long-term antipsychotic therapy of patients with schizophrenia, which can be considered as one of the variants of neuroleptic disease, this severe iatrogenic multiple organ pathology, due to a wide range of the negative side effects of antipsychotic drugs.

**Keywords:** Antipsychotic drugs; side effect; kidney amyloidosis

## Introduction

The problem of amyloidosis is one of the urgent problems in biology and medicine (1-3). Modern ideas about amyloid genesis suggest the production of a special amyloid precursor protein under the influence of the so-called amyloid-releasing factor produced by macrophages due to a genetic defect or under the influence of a stimulating agent (4). It is believed that various defects in the body's immune system lead to the formation of amyloidosis (5). However, it has long been known that many antipsychotic drugs (AP) have a certain immunotropic activity, changing the permeability of cell membranes, including immunocompetent cells (6). In this regard, the data on a statistically significant increase in the frequency of brain amyloidosis in patients with schizophrenia are noteworthy (7). These facts in relation to the problem of amyloidogenesis are of particular interest. It is believed (8) that the pathogenesis of cerebral amyloidosis is close to that of AA-amyloidosis, the main target organ of which is the kidneys (nephropathic amyloidosis) (1,2). One of the main links of AA-amyloidogenesis is the active participation of monocytic phagocyte elements in the process (2,3,9). In particular, phagocyte cytomembrane enzymes play an essential role (2,10). A certain correlation between the content of serum amyloid protein in the blood and the state of monocytic phagocyte and lymphocyte systems was also established (2,9).

Thus, AP, affecting the immune system, by their pharmacological and biological properties may well be amyloidogenic agents (11). However, amyloidosis, etiologically caused by the use of drugs, including AP, is practically not described. In this regard, the data analysis of the observations neuroleptic amyloidosis of the kidneys, the main criteria for diagnosis was:

- a) prolonged antipsychotic therapy (APT) primary mental illness
- b) absence of somatic pathology, complication which could be amyloidosis
- c) morphological and histochemical properties of amyloid, characteristic of secondary AA-amyloidosis.

## Material and methods

The case histories and autopsy materials of patients with schizophrenia who died in the Tver regional M. P. Litvinov's psychiatric hospital № 1 from 1952 to 2011, in which an autopsy was found amyloidosis of the kidneys. According to the given diagnostic criteria, 12 observations were identified. Archival micropreparations after appropriate treatment were again stained with an alkaline solution of congo red and studied in polarized light. The autoclave method proposed by T. Kitamoto and co-authors (1986) (12) was used to verify AA-amyloidosis.

## Results

Of the 12 deaths, there were 6 men and 6 women aged 19 to 67 years. The median age was 42 years for males and 53 years for females. The period from the beginning of APT to the appearance of persistent urinary syndrome is from 40 to 296 months, on average, about 15 years. In all cases, there was a fairly typical clinic for the development of nephropathic amyloidosis. Manifestation of the disease in 11 patients began with isolated urinary syndrome. Only 1 patient aged 49 years immediately developed a complete nephrotic syndrome with a rapid increase in edema. However, 7 of

the 11 mentioned patients subsequently also developed complete (edematous) nephrotic syndrome. Term of occurrence of edema after detection of persistent changes in urine from 4 to 8 years. In 3 patients, edema was initially transient and only eventually became permanent. Blood pressure in 11 patients was constantly within the normal range or even slightly lowered. Only 1 examined person had hypertension with figures 160/110-190/100 mm Hg 2 months before death. Persistent proteinuria was observed in all patients, but its level was different. In 1 patient, the protein content in the urine was only 0.033‰, in 3 it did not exceed 0.33‰, in 2-1,65‰. Most often, the maximum level of proteinuria was kept within 3.3‰ (4 patients), sometimes reaching 6.6‰ (2 patients). Daily protein loss was determined only in 2 people. It was 2.4g and 3.3g.

A constant phenomenon was a small persistent leukocyturia. The number of leukocytes in the field of vision ranged from 1-2 to 6-8. Hematuria was observed in 8 patients, was unstable and very moderate (the number of red blood cells from a single to 2-4 in the field of view). Transient small cylindruria was observed in 9 patients. Cylinders were, as a rule, hyaline and granular, occasionally waxy, their number in the field was of view to 2-3, sometimes 5-6. The described features of urinary sediment are considered typical for urinary syndrome in renal amyloidosis (13,14). In clinical blood tests in all patients revealed moderate hypochromic anemia. Attention is drawn from the very beginning of treatment with AP constantly accelerated ESR (on average, up to 25mm/h), which indirectly indicates certain shifts in homeostasis. Moreover, in recent years of the disease in the presence of persistent urinary syndrome (ie, essentially, kidney amyloidosis), the average value of ESR was about 45mm/h. A similar phenomenon in renal amyloidosis is known from the literature (3,13).

Changes in blood biochemical parameters are essential and typical for nephrotic syndrome. Thus, hypercholesterolemia was recorded in 7 out of 10 examined patients. The maximum cholesterol level was 17.2mmol/l, the average value of 8.58mmol/l. Fibrinogen blood was determined in 5 patients and in all cases was increased. Its average level is 6.58g/l with fluctuations from 4.44 to 9.32g/l. Seriously disturbed protein metabolism. Studies were conducted in 6 patients. All of them show pronounced hypoproteinemia. By the time of death, the total protein content in the blood fell to 38g/l in 1 patient, to 40-44g/l in 4 patients and only 1 was only slightly below normal (62.7g/l). At the same time, all the examined patients had significant dysproteinemia. Thus, the average content of albumins was 39%, globulins-61%. A/G coefficient is significantly reduced (average-0.7). The study of globulin fractions showed a relatively normal content of alpha-globulins and the rise of beta- and especially gamma-fractions. The averages are 17.5%, 14.8% and 23.9%, respectively.

Nitrogen-excreting renal function persisted for a long time. The level of residual nitrogen, urea and creatinine in almost all patients remained within the normal range. Only 4 patients in the last month before death slightly increased blood levels of urea and creatinine (to 8.5-15.8 mmol/l and 125-135 mmol/l, respectively). However, the Rehberg test conducted in 2 patients showed a decrease in glomerular filtration (up to 60.2 and 75ml/min) and tubular reabsorption (up to 85-86%).

Ultrasound examination of the kidneys was performed in 4 patients and 3 of them repeatedly. Diffuse changes in renal parenchyma were noted in all findings. The patients died from various causes. In proteinuric stage of renal amyloidosis died 5 patients, in nephrotic one-6; in 1 patient was observed a transition in nitrogenemic stage. During the period of the developed nephrotic syndrome all six patients died from the increasing heart failure. A similar mechanism of death in renal amyloidosis is well known (3,14). Two died from acute pneumonia and coronary pathology, one from hemorrhagic stroke and drug toxicoderma, which is described in the literature as a result of side effects of chlorpromazine (15). The section revealed a typical pattern of renal amyloidosis. In 10 deceased patients it was the so-called big greasy buds, their weight ranged from 480 to 960 g. In 2 cases the kidneys were amyloid wrinkled (weight 300 and 340g). In 3 cases, in addition to the kidneys, the spleen was affected by amyloidosis, and in 1 of them the liver was also affected. Microscopically, congophilic amyloid masses were found in the capillary loops of the glomeruli and in the vessel wall. The intensity of amyloid deposition in glomeruli ranged from focal to total lesion. In this case, the severity and prevalence of the process correlated with clinical stages, as well as with the duration of APT. Thus, with a period of treatment of more than 15 years, total defeat of the vast majority of glomeruli was revealed in all cases, and with a period of less than 15 years only in 2 of 6 ones. In polarized light, the characteristic dichroism of amyloid was detected in the form of a light greenish glow. During denaturation of amyloid by means of temperature action (autoclaving of sections before painting the congo red at a temperature of 130°C) according of the method of T. Kitamoto and co-authors (1986) (12) its tinctorial properties were lost within 30 minutes, which is inherent in AA-type amyloid (12, 16).

## Discussion

Thus, in the described observations after prolonged APT a fairly typical clinic for the development of nephropathic amyloidosis was noted. As a rule, it manifested as an isolated urinary syndrome, which subsequently turned into a complete nephrotic syndrome with edema, increasing hypo- and dysproteinemia, hypercholesterolemia and hyperfibrinogenemia in more than half of patients. In this case, there was usually no hypertension and severe azotemia. Morphologically, the process in the kidneys was verified as secondary nephropathic AA-amyloidosis. In our opinion, neuroleptic amyloidosis is a form of neuroleptic disease, caused a wide range of the negative side effects of AP and including such pathology as neuroleptic cardiomyopathy, sudden cardiac death, neuroleptic malignant syndrome, neurological extrapyramidal disorders, metabolic syndrome, endocrine dysfunction, toxicoderma, disorders of leukopoiesis, cholestatic hepatitis, etc (17).

## Conclusion

So, the described cases of renal amyloidosis, developed in the process of APT, show the possibility of developing this pathology as a result of long-term administration of AP. This kidney damage is quite logical to consider one of the manifestations of the so-called neuroleptic disease. The appearance of clinical and laboratory signs

of renal pathology in patients receiving long-term AP, should alert physicians in terms of the development of neuroleptic amyloidosis.

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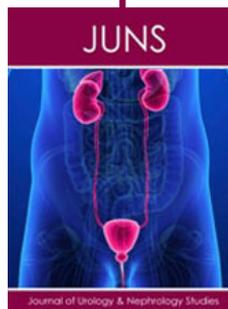
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