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Neurological findings in autosomal dominant polycystic kidney disease

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ABSTRACT

Objective: Autosomal dominant polycystic kidney disease (ADPKD) mainly affects the kidneys, but other abnormalities like intracranial aneurysms (ICAs) are not uncommon. In this study, we aimed to investigate retrospectively frequency of ICA and other neurological abnormalities in ADPKD patients.

Methods: One hundred and forty patients with ADPKD who did not receive replacement therapy and followed-up at outpatient clinic were evaluated.

Results: The mean age of the patients was 43.4 ± 13 years and mean glomerular filtration rate was 87 ± 15 ml/min. ICA was detected in four (2.8%) patients. Three patients were from the same family. Thirteen (9.3%) patients had magnetic resonance angiography due to their family stories, but aneurysm was not seen in them.

Conclusion: Individuals with ADPKD who have a history of aneurysm or hemorrhage in their family should be screened for aneurysm due to mortality and risk of recurrent rupture.

Keywords: Autosomal dominant, polycystic kidney disease, intracranial aneurysms, arachnoid cysts

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Autosomal dominant polycystic kidney disease (ADPKD) is a genetic systemic disease that characterized by cysts in kidneys and other organs like liver, pancreas, brain and vascular bed. The gene that mostly (in 85% of the cases) causes the disease is polycystic kidney disease 1 (PKD1) gene on the short arm of chromosome 16 (16p13.3). In 15% of the cases, polycystic kidney disease 2 (PKD2) gene on the long arm of chromosome 4 (4q21) results in ADPKD. Both genes are pleiotropic and influence many phenotypic characteristics. For instance, abdominal hernias, mitral valve prolapse, aorta dilatation and intracranial aneurysms (ICAs) can be observed clinically in the ADPKD cases. Frequency of ICA varies depending on the family history and was reported to change between 6% to 20% [1, 2]. Arachnoid cysts (8%) and meningeal cysts (2%) are other structural abnormalities of central nervous system (CNS) [3, 4]. The most feared clinical picture of ICA is rupture. Although localization, size and rupture story determine prognosis, there is no sufficient data about this issue in ADPKD [5]. It was reported that rupture risk of ICA increases fivefold in ADPKD patients compared to overall population. Family clustering of ADPKD patients with ICA story is apparent, but the presence of ICA among the family members who have the disease is heterogeneous. Besides, the frequency of ischemic stroke is expected to rise in ADPKD cases because of the increased cardiovascular risk. In this study, ADPKD patients were investigated with regard

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to CNS abnormalities. Such abnormalities detected with imaging methods were analyzed as well.

METHODS

One hundred and forty patients who were conclusively diagnosed with ADPKD based on the family story, clinical findings and imaging methods and consulted to outpatient clinic of Uludağ University Scool of Medicine Nephrology Department were evaluated retrospectively in the study. The patients who underwent renal replacement therapy were excluded from the study, since they would not be followed-up at outpatient clinic. Ultrasound criteria suggested by Pei *et. al.* [6]. were used as diagnosis criteria of ADPKD. Over the course of routine outpatient clinic controls, all of the patients were investigated with regard to possible extrarenal findings, comorbid diseases, smoking history, family history of sudden death, presence of ICA and history of cerebrovascular disease. All of the patients with ICA story in family have been screened with magnetic resonance angiography. The cases that contain aneurysm were consulted to Neurosurgery department.

Statistical Analysis

As part of statistical analysis, descriptive analyses were performed with SPSS version 22. Variables were given as mean ± standard deviation.

RESULTS

The mean age of the patients was 43.4 ± 13 years. There were 61 males and 79 females. Sixty-eight percent of the patients did not have smoking history. Hypertension was not detected in 33.6% (n = 47) of the patients. Of the whole group, 44.3% (n = 62) had controlled hypertension and 22.1% (n = 31) had uncontrolled hypertension. Fifty-five (39.3%) patients were found to have liver cyst which was the most common extrarenal finding (Mean age: 47 ± 12 years, 36 females, 19 males). Mean glomerular filtration rate was 87 ± 15 ml/min. In terms of neurological findings, ICA was seen in four (2.8%) patients. The aneurysms detected were saccular with a mean diameter of 4.5 mm. In three patients, they were located on the right and left middle cerebral artery. One patient had aneurysm on posterior inferior cerebellar artery (PICA). This patient who was determined to have 3.5 mm aneurysm on the left and 4.5 mm on the right admitted to the hospital due to bleeding stroke. He died within one month following the operation. Of other three patients, two underwent an operation in which elective clamp was placed, and one had clamped after hemorrhage. Follow-up of these three patients, who were operated electively or emergency have shown no sign of neurological deficiency. Thirteen (9.3%) patients had magnetic resonance angiography due to their family story of ICA, but no aneurysm was detected. With respect to other neurological findings in history, one patient had subdural hematoma, two patients had arachnoid cyst and two patients had epilepsy. Oligodendroglioma was reported (WHO grade 2) in a patient with epilepsy history in frontal region. The patient had postoperative radiotherapy and followed-up without any neurological deficiency. As part of the investigation about cerebrovascular disease, only one patient was detected to have a story of ischemic stroke. Two patients were examined because of headache. Pituitary macroadenoma was observed in one patient, but the lesion with spontaneous shrinking size was interpreted as pituitary cyst. Other patient was diagnosed with migraine.

DISCUSSION

In our series, aneurysm frequency of ADPKD patients followed-up was lower than that of literature. However, compared to overall population, it was supposed to be higher. This finding may result from the exclusion of the patients who had renal replacement therapy [7]. The findings such as age of onset, hypertension and uremia which are not specific to the disease may improve cerebral hemorrhage risk. It is consistent with literature that the patients who were determined to have aneurysm rupture and asymptomatic aneurysm were in the same family. Intracranial vascular imaging is essential especially for these patients with story of ICA rupture. In literature, it is reported that ADPKD patients with ICA rupture had a mortality rate of 50% [5, 7, 8]. If ADPKD patients whose genetic penetrance are 100%

Table 1. Type and location of intracranial aneurysm

Cases	Initial presentation	Location	Diameter (mm)	Outcome
1	Subarachnoid hemorrhage	Left and right PICA	5.5/3.5	Death
2	Subarachnoid hemorrhage	Anterior	3	at follow-up no neurological deficit
3	Elective surgery	Anterior	35	at follow-up no neurological deficit
4	Elective surgery	Anterior	3	at follow-up no neurological deficit

PICA = posterior inferior cerebellar artery

had family stories of sudden death, they can be investigated with regard to presence of ICA. This slowly progressive disease and the emergence of renal failure after the fifth decade make us think that premature death cases seen in the families of patients may result from ICA rupture. In line with this observation, the aneurysm rupture in ADPKD is experienced at a younger age compared to overall population [9]. In general, ICAs seen in ADPKD cases are detected in anterior circle of Willis [3]. In our study, the aneurysms determined in all cases, except one were in the anterior circulation. In a recent meta analysis which evaluated ADPKD with 563 aneurysms, mean diameter of non-ruptured aneurysm was 4.4 mm and the middle cerebral artery was the main location among half of the patients [8]. In three of our patients, the involvement location was the right and left middle cerebral artery and the diameter of aneurysm was lower than literature (Table 1). There was only one posterior circulation aneurysm that located at PICA, was died. Different aneurysm location of that patient who was in the same family with other two patients make us think that rupture risk may differ despite the presence of aneurysm in the same family. In a case in which pituitary macroadenoma was detected and hormone profile is normal, diameter of adenoma shrank and the lesion was considered as a cyst later. Therefore, we speculated that most of the extrarenal findings in those patients may be associated with PKD1 gene or PKD2 gene.

CONCLUSION

In conclusion, our results confirm that ICA bleeding in ADPKD patients tends to cluster in families and family history is so important and can provide invaluable information about rupture risk.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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