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**Update on diagnosis and treatment of pulmonary alveolar microlithiasis**

Wang HY *et al.* Update on PAM

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**Abstract**

Pulmonary alveolar microlithiasis (PAM) (MIM265100) is a rare disease characterized by the diffuse deposit of microlithiasis in alveolar spaces. PAM could occur worldwide with high prevalence in Asia and Europe. Familial occurrence indicates its autosomal recessive trait and the *SLC34A2* gene was identified as the responsible gene for the disease. In spite of the versatile mutation sites in patients from other countries, exon 7 and exon 8 might be the most liable gene in Chinese and Japanese patients. Most mutations caused the premature termination of proteins and produced truncated proteins, leading to the blocking of the recycling and degrading of outdated surfactant which full of phospholipids. The most outstanding clinical feature of PAM is the discrepancy between the paucity of symptoms and the degree of pulmonary involvement. Diagnosis is easy to establish based on typical chest radiograph image and nuclear medicine improves its early diagnosis and active evaluation. Pathology of the unique intra-alveolar lamellar microliths gives strong support for diagnosis. No effective treatment is considered valid currently. However, lung transplantation is effective for advanced-stage patients, and long term treatment of disodium etidronate seems promising.

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**Key words:** Pulmonary alveolar microlithiasis; *SLC34A2*; Mutation; Chest computed tomography; Treatment

**Core tip:** Pulmonary alveolar microlithiasis (PAM) is a rare disease and lack of enough acknowledgements. The present review provides a comprehensive description on the latest progress in the genotype and treatment of PAM. *SLC34A2* is identified as the responsible gene and its mutation in patients from different countries has showed versatile symbols, whilst Chinese and Japanese patients only involved exon 7 and exon 8. The diagnosis of PAM could be established on typical chest radiograph image. Though currently no effective regimens are valid to cure the diseases, long term treatment of disodium etidronate seems promising.

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**INTRODUCTION**

Pulmonary alveolar microlithiass (PAM) (MIM265100) is a rare disease characterized by the diffuse deposit of microlithiasis in alveolar spaces[1]. Ever since its first description by Malpighi in 1686 and nomination by Puhr[2] in 1933, cases of PAM have been reported all over the world successively, including several reviews with large size of cases[3-5]. Those reports play an important role in the acknowledgement of epidemiological, pathological, radiological and clinical feature of PAM. However, those reviews usually only collected cases written in English for analysis, and many cases such as Chinese patients that written in local language were unfortunately ignored. Thus the recognition of PAM is unavoidably biased. Moreover, the recent identification of the responsible gene, *SLC34A2*, and update of long term follow-up sheds new light on its genetic etiology and therapy. The present review summarizes the recent findings of the disease mainly focusing on genetic etiology, clinical diagnostic methods and therapy regimen, together with the data from Chinese patients of PAM, aiming to provides more comprehensive view of PAM.

**UPDATE ON EPIDEMIOLOGY**

PAM occurs worldwide. According to Mariotta’s report in year 2004, in which 576 cases in international literature from 51 countries were reviewed, Europe was the most prevalent continent and Turkey had the highest number of PAM patients[3]. Whereas the prevalence in Asia was severely underestimated for many cases published in local journals were unavailable for analyzing. For example, Tachibana *et al*[4] reported 105 cases in Japan by year 2001, while only 32 cases were obtained in international literature. The same condition happened in Chinese data, even more severe. Recently, we searched Chinese cases of PAM and obtained 200 cases since the first cases reported in 1965. Combined with Tachibana’s data, it seems the prevalence of PAM in Asia is actually significantly higher than Europe and China is also one of the countries predominated with PAM. Yet, no evidence demonstrates regional clustering of patients in China either.

Average familial occurrence is about one third of 576 cases[3]. Whilst, the ratio is significantly higher in those countries with high number of cases, such as Japan (50% of 111 cases)[6], Turky (48% of 52 cases)[1], Italy (43.7% of 48 cases)[5] and China (56% of 200 cases). The feature that those familial patients are horizontal siblings from inbred families strongly indicates its autosomal recessive trait. However, even putting into the consideration of the low rate of family screen, there still are large parts of sporadic patients.

The age at diagnosis of PAM varied from neonatal to eighties. But most patients are found at the second or third decade. Japanese patients are the youngest group with 52.3% under 15[6], the mean age of patients in other countries are at twenties. And Chinese patients showed 10-year delay of age at diagnosis, which is probably due to the low international healthcare and routine checkup. Sex difference was not seen at prevalence, diagnosis age and progression in most areas, except for China and Turkey where male patients had high prevalence[1].

**UPDATE ON GENETIC AND MECHANISM**

Though PAM has been postulated as an autosomal recessive disease, it was until year 2006 that Corut *et al*[7] first identified a PAM locus to chromosome 4p15 by homozygosity mapping, and suggested that the *SLC34A2* gene cause PAM through the genotyping and linkage analysis study on a larger Turkey family. Meanwhile, Huqun *et al*[8] employed a modified homozygosity mapping method and discovered homozygous exonic mutations on exon 8. They further confirmed this conclusion through the function assay of mutant protein *in vitro*. Therefore, the *SLC34A2* gene was identified as the responsible gene for PAM. And the following articles described versatile mutation symbols of the *SLC34A2* gene in 14 PAM cases mainly from Turkey, China and Japan, as we analyzed previously[9-17]. These mutations demonstrated point deletion[7,14], pointed mutation[7,9,14-16], deletion plus insertion mutation[8], small fragment deletion and target fragment deletion[11]. Most of these mutations involved the exons and homozygous mutation is the common character of these studies. However, a significant phenomenon needs to be noted is that the mutations in Turkish patients happened on several exons, whilst only exon 7 and exon 8 are affected in Chinese and Japanese patients. Especially in China, two positive reports of studies that performed genotyping in PAM patients, found homozygous mutations on exon 8[12,13,15]. Moreover, we recently found a compound heterozygous mutation from a sporadic Chinese patient also showed an involvement of exon 8[18]. Therefore, we hypothesize that exon 8 might be the most vulnerable site in Chinese patients, surely more case studies or experiments are needed to confirm it.

Despite the versatile symbols most mutations caused the premature termination of proteins and produced truncated proteins through either affecting the protein produce or abolishing gene expression. *SLC34A2* is a type IIb sodium phosphate co-transporter primarily expressing in alveolar type II cells, and the only known sodium-dependent phosphate transporter expressed in the lung[19]. This protein plays the role of clearing the phospholipids the alveolar space through transporting the phosphorus ion into the alveolar type II cells. The mutated proteins lose their function and lead to the blocking of the recycling and degrading of outdated surfactant which full of phospholipids, which finally results in the formation of microliths.

However, the molecular structure-function relationship of this protein is still poor understood. While back to previous reports of PAM, only Hunqun *et al*[8] performed the function study of the expressed protein through the assay of phosphate uptake by Xenopus oocytes, which was microinjected with transcribed *in vitro* wild-type RNA or mutant RNA of *SLC34A2*. Even though, it only confirmed the association of *SLC34A2* in this disease, but didn’t demonstrate the relative function region of the protein or the mutant. In our recent investigation, we took the advantage of bioinformatic technology and predicted the 3-D structure using online software, demonstrated the main functional domain of wild type NaPi-IIb and the possible transportation sites through the summary of changes in different mutants[18]. Though the 3-D structure prediction exits unavoidable errors, it still could be a good tool for the investigation of the molecular-function relationship of this protein.

It was speculated whether genotype-phenotype correlation exists in PAM patients. The evidence for that seems lack from the existed reports despite the full penetrance of genetic defect. On the contrary, exogenous factors seem play an important role in the progression in this disease of early onset and very slow development. Heavy smokers seem to have severe phenotype. Infection also accelerates the progression. Recently, de Laurentiis *et al*[20] studied the pulmonary cell immune phenotype and concluded that CD8+ has the prevalence in the BALF of PAM patients.

**UPDATE ON CLINICAL FEATURE**

The most outstanding clinical feature of PAM is the discrepancy between the paucity of symptoms and the degree of pulmonary involvement. The patients of PAM are usually free of symptoms when discovered fortuitously for other diseases or by mass radiograph examination. The disease progresses very slowly, even to 30 years, to appear exertional dyspnea or cough[21]. Lung function keeps normal or slight impaired ventilatory function or diffusing capacity. Whereas, at the advanced stage of the disease, the severe deposits of microstones impaired the gas exchange function of alveolar space and resulted in respiratory insufficiency.

Diagnosis is easy to establish based on the typical chest radiograph. Chest X-ray usually showed bilateral fine sand-like micro-nodulation of calcific densities throughout both lung fields mainly involved the middle and lower zone, sometimes producing a “sand-storm” appearance. On high resolution computed tomography it presented the wildly diffused microliths deposite in airspace, which caused consolidation of the affected area. High density calcification of this consolidated area, mediastinal window, and pleura together with interlobular septa shaped as a contour. This unique manifestation of radiograph makes it a strong method in detecting of PAM patients, for most of those patients are not aware of their disease without clue of symptoms. The magnetic resonance of imaging with the hypointensity or a signal void on T1- and T2-weighted images of the calcification lesions provides little value in PAM, while the development of nuclear medicine gives more help on the contrary. The absorption of Tc-99melabeled diphosphonate compounds, which have a natural affinity for calcification foci at the soft-tissue level, help to detect early pulmonary calcification[22]. And the uptake of 18F-fluo-rodeoxyglucose on combined positron emission tomography/computed tomography may be useful to evaluate the pulmonary inflammation or predict the prognosis of the patients of PAM[23,24].

Microliths in following sputum or bronchoalveolar lavage under bronchoscope examination then give strong support for diagnosis. Pathology of lung biopsy and autopsy specimens are important for prove of diagnosis but not necessary. It demonstrates the unique intraalveolar lamellar microliths, which is highly correlated with CT findings[25]. Chemical analysis revealed that these microstones consist of calcium and phosphates. Nevertheless, genotyping assay of *SLC34A2* could further clinch the diagnosis.

Blood tests including serum calcium and phosphorate concentration and different steroids are unremarkable, since only the imbalance of calcium and phosphorate only happened in microenvironment of alveolar space. Serum surfactant proteins A and D were discovered remarkable elevation in parallel with the deterioration of the lung function[26]. Therefore, they were suggested as the candidate marker for monitoring the activity of the disease.

Comorbid or extrapulmonary calcification is not common. Though there are some reports of associated milk alkali syndrome, mitral stenosis, pericardiac cyst, *etc*[27-29]. The study of the mutation in *SLC34A2* also explained some extrapulmonary calcification such as testicular microlithiasis[7], or the development of aortic valve calcification and arteriosclerosis[30].

**UPDATE ON LONG-TERM THERAPY REGIMEN**

No effective treatment is considered valid currently. Though developing slowly, one of our patients even achieving spontaneous remission[31], the long-term prognosis of the disease is poor. Most patients died of respiratory failure resulting from the chronic interstitial inflammation and fibrosis finally. The removal of microlithiasis *via* repeated bronchoalveolar lavage without improvement in radiography was not as effective as it in pulmonary alveolar proteinosis[32].

 Lung transplantation has been thought the only expecting regimen especially for patients with severe respiratory failure and right heart failure. The transplantation has demonstrated good effects on the regression of right heart failure[33]. However, most transplantation is bilateral to avoid the persistent shunting of blood, which also limited its application. The reported data is very limited and lack of the long term follow up. The longest follow up duration is 15 years after lung transplantation[34]. Thus, the timing for surgery and the possibility of reoccurrence in the future are still needed to be considered.

Disodium etidronate, a diphosphonate, has been used to treat PAM for many years. Ozcelik *et al*[35] first introduced it to treat patients of PAM for its role of inhibiting the formation of new pulmonary calcium-phosphate crystallization and resolving previously formed calcifications, and gained clinical improvement and radiological stabilization. The following clinical trials with little or no benefit questioned this regimen[36,37]. However, Ozcelik *et al*[11] recently published their new reports describing the beneficial effects of long-term treatment (9 and 11 years of treatment, respectively) with disodium etidronate in two cases with PAM diagnosed in childhood. They considered that the factors such as the onset of initial treatment, duration and the dosage of the medicine could influence the result of the treatment.

However, in most of Chinese patient who always attacked by acute infection, active treatment of antibiotics and bronchial dilator results in quick improvement and prevention for further deterioration.

**CONCLUSION**

PAM is a rare genetic disease with aotosomal recessive trait occurring worldwide. The *SLC34A2* gene was considered as the responsible gene and exon 8 was the most liable mutation sites in Chinese patients. The mutation usually caused the premature termination of protein and produced truncated protein to induce the accumulation of microliths in alveolar space. The most outstanding clinical feature of PAM is the discrepancy between the paucity of symptoms and the degree of pulmonary involvement. Diagnosis is easy to establish based on the typical chest radiograph. But the nuclear medicine improves its early diagnosis and active evaluation. No effective treatment is considered valid currently. However, lung transplantation is effective for advanced-stage patients, and long term treatment of disodium etidronate seems promising.

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