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Does transthyretin function as one of contributors for preeclampsia?

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SUMMARY

Preeclampsia (PE) is a multi-system disorder of pregnancy, which is characterized by new onset hypertension and proteinuria, resulting in multi-organ damages within a potential procedure. However as a worldwide leading cause of maternal and fetal mortality and morbidity, the precise origin of PE has not been clarified yet, which also makes obstacles to the management of the disease. Transthyretin (TTR) is a special protein involved in amyloid diseases, has important effects on amyloid fibrils formation. We assumed that TTR might cause a disorder of maternal vascular function and contributed to the pathology of the disease by deposition of TTR amyloid fibrils in the vascular system, which are produced by variant TTR proteins, resulting in organ ischemia. If this hypothesis proves to be correct, this variant may be of diagnostic importance as novel biomarkers for the disease, in addition, it might also benefit to the management of PE.

Introduction and background

PE is a multi-system syndrome of pregnancy, characterized by a sudden occurred hypertension, and the appearance of proteinuria and edema after 20 weeks of gestation, combining with brain, heart, renal and liver damages. PE is a leading cause of maternal and fetal/neonatal mortality and morbidity worldwide, occurring in 3–5% of pregnancy.[1,2] Presently, although the etiology of PE has not been clarified yet, it has been proved that genetic susceptibility, placental ischemia and inflammatory response are involved in the origin. According to Williams Obstetrics, genetic factors may be relevant to the cause of PE. Although some gene locuses have been found related to origin of the disease, it still far from enough to give a fulfilled explanation for the cause of PE. [3]The mainly pathological changes in PE is maternal vascular dysfunction that induces placenta ischemia and multi-organ disorders, which has been regarded as the basic pathophysiological alternation in PE [1–3].

TTR is a tetrameric serum protein of four identical subunits (55 KDa), synthesized mainly in the liver, eye and choroid plexus, but also placental trophoblasts, belongs to a group of proteins including thyroxine-binding globulin and albumin which bind and transport thyroid

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Conflict of interest
None declare.

hormones in the blood, and its main function is the transport of thyroxine (T₄) and vitamin A (retinol) associated with the retinol binding protein [4,5]. It has been reported that mutations of the amino acid sequence of TTR are of clinical interest. The variant TTR proteins make amyloid deposits in familial amyloidotic polyneuropathy (FAP), Systemic Amyloidosis and other amyloid diseases. However the mechanism of amyloid deposit is not clear [6,7].

Transthyretin in amyloid diseases

Amyloid diseases belong to autosomal dominant hereditary diseases characterized by the deposition of amyloid fibrils in viscera (heart, gastrointestinal organs), the peripheral nervous system, and vascular system [8–10]. It is caused by different type of amyloidosis, at least 20 different amyloidogenic proteins have been recognized, TTR is one of the most common amyloid protein [6]. The TTR variants have mostly been associated with variable degrees of cardiac and neural tissue amyloid deposits. Over 80 different TTR mutations have been reported associated with amyloid diseases and exhibit tissue-selective deposition [11]. TTR V30 M has been confirmed to be a contributor of familial amyloidotic polyneuropathy (FAP), deposits of wild-type TTR appear to cause senile systemic amyloidosis (SSA), and TTR Thr45, TTR Met111, TTR V122I and TTR Lys92 mutations are associated mainly with cardiac disease [12–14]. Amyloid diseases can be induced by various conformational changes in this protein. Why mutated TTR deposits in the form of amyloid is unknown, but it has been reported that the tetramer dissociation into a nonnative TTR monomer with low conformational stability may be attributed to the pathology changes, which results in partially unfolded monomeric species with a strong tendency to aggregate in tissues with subsequent visceral, peripheral, autonomic nerve, and vascular dysfunction [13,15]. Presently, it is about a quarter to half of patients with primary amyloidosis are involved in symptomatic cardiac amyloidosis, and a cardiac cause of death has been the most common amyloid related death in primary amyloidosis, in the form of congestive heart failure, arrhythmia and so on [10,12]. Intramural amyloid deposits cause stenoses and obstructions in coronary arteries and may lead to ischemia disease. Meanwhile, systemic vascular injury is also involved and often leads to obstruction and consequent ischemia. Amyloid often selects the media and adventitia to large arterioles and small arteries, making vascular wall thickened, contributing to organ ischemia [10,16]. According to a study for leptomeningeal amyloidosis, TTR amyloid deposition was found within the leptomeningeal vessel walls, which is another evidence for the vascular pathology changes in amyloid disease [17].

Possible effect on transthyretin amyloid fibrils formation

Although the process of amyloid fibril formation remains vague, some factors have been confirmed to have effect on the amyloid formation. Presently, inflammatory response has been proved to be associated with amyloidosis, casual relationship between deposition of amyloid fibrils and acute phase protein has been reported. Many studies have supported the relationship between serum amyloid A and deposition of reactive amyloid in patients with chronic arthritis, tuberculosis or familial Mediterranean fever [18]. TTR is one of the negative acute phase proteins involved in amyloid diseases [19]. However, the mechanism of amyloid formation associated with inflammatory response has not been clarified yet.

According to some studies, PE has previously been ascribed to an excessive maternal inflammatory response in pregnancy, indicated that it might induce an aggregation of TTR fibrils [20]. Another factor supposed to be associated with TTR amyloid formation is oxidative stress. Placenta ischemia ascribed to abnormal cytotrophoblast invasion may arouse an oxidative stress state, which can lead to a widespread maternal inflammation [1,2,21]. TTR monomers are the results of different oxidizing reactions. Some oxidized TTR isoforms may be linked to the modifications of TTR as well as amyloid formation [19]. Oxidized TTR has been found in amniotic fluid of PE [22].

Hypotheses

We assume that TTR as one of proteins related to amyloid diseases may serve as a contributor to pathology of PE. Patients with PE may involve in series mutations of some gene locuses, including the TTR gene mutations.[8]One or more toxic variant TTR proteins especially associated with amyloid formation in PE may be produced, TTR tetramer dissociation and leads to partially unfolded monomers that aggregate into amyloid fibrils, the TTR amyloid fibrils deposit in the maternal vascular system and various organs [16,23]. A dysfunction of maternal vascular system might be induced, resulting in systemic vascular spasm, then there appears organs ischemia (placenta, liver, renal and so on) and the clinical demonstrations of the disease. An oxidative stress may be caused by organs ischemia (placenta ischemia) and the higher oxidative stress in PE could be another destabilizing factor of TTR tetramer which might also stimulate the dissociation of tetramer into partially unfolded monomers which may aggregate in selected organs [6,20]. Oxidative stress may be regarded as a leader to the excessive maternal inflammatory response which might put positive effect on the TTR amyloid formation, meanwhile [18,21]. (Fig. 1) If this hypothesis proves to be true, variant TTR might serve to be a contributor to the pathology of PE. Nevertheless, how the TTR protein tackle with the maternal vascular system remains obscure, future work is required.

Future work

Our hypotheses indicate TTR protein might take a part in the pathology of PE. However, there are still some questions to be resolved. A biopsy diagnosis was found to be a safe and effective method for assessing amyloid involvement, and is needed to provide an effective evidence for the hypothesis [10,16]. In addition, Immunohistochemistry might catch TTR proteins in maternal tissue, and find out whether it can be located in vascular system. Genomics may help to find variant TTR genes and confirm the assume [1]. Then an animal model could be established and the whole pathology process might be imitated. If it is proved, there might present an alteration of TTR serum concentrations. As written, we consider that some variant TTR proteins may contribute to the deposition of amyloid fibrils in the vascular system, serum TTR monomers aggregate to form amyloidosis, which is assumed to lead to a decrease levels of TTR compared to the women with healthy pregnancy. Besides, liver and placenta ischemia may cause a decrease secretion of TTR [24,25]. Despite the development of obstetrics and neonatal care, there is a need for biomarkers of high predictive value for early diagnosis of the disease. TTR might serve as a candidate. With the development of proteomics, further research may get a nice result in this

field [26]. Presently, TTR amyloidosis has been confirmed to be attributed to the unstable form of TTR tetramer, stabilizers and inhibitors have been found to prevent the fibril formation. Several small compounds, such as diclofenac, flufenamic acid and diflunisal have been considered to stabilize TTR [27]. According to the study, diflunisal derivatives function as TTR stabilizers and inhibitors of fibril formation though the selectivity of binding to TTR at T4 binding sites and other inhibitory step of fibrillogenesis [28,29]. In the present work, greatly improved inhibitors have been designed and the new TTR fibrillogenesis inhibitors are based on the diflunisal core structure which has been registered as a drug of nonsteroidal antiinflammatory drugs (NSAIDs) undergoing clinical trials for TTR amyloid diseases [30]. It must be taken into consideration in the further testing of drugs for the treatment of TTR amyloidosis. And if our hypotheses prove to be true, inhibitors of TTR amyloidosis might also contribute to the management of PE.

Conclusion

As above, our new hypotheses might be another explanation to the pathophysiology of PE. These findings provide insight into a novel pathophysiological mechanism of PE related to TTR and may offer, in the future, new therapeutic opportunities.

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Fig. 1. The new hypotheses for pathology of PE. An introduction of how TTR contributes to the pathophysiology of PE.