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The role of vitamin K in the etiology of diffuse alveolar hemorrhage

Aalt Bast [1,2,3], *Marjolein Drent*[1,3,4]

[1]Dept of Pharmacology and Toxicology, Faculty of Health, Medicine and Life Science, Maastricht University, Maastricht, the Netherlands; [2]Venlo Campus, Maastricht University, Venlo, the Netherlands; [3]ild care foundation research team, Ede, the Netherlands; [4]ILD Center of Excellence, St. Antonius Hospital, Nieuwegein, the Netherlands

With great interest, we have read the paper by Alexandre et al. (1).

They investigated Diffuse Alveolar Hemorrhage (DAH) in various disorders and concluded that "DAH appears to be a heterogeneous syndrome". The authors could not define a common pathway for DAH.

We would like to emphasize that in our opinion the underlying disorder is not the cause for DAH. DAH rather needs to be considered as an accompanying symptom. In other words, DAH is in all cases only a symptom associated with the diseases. We suggest that often, the pathophysiological basis for DAH is the same, *viz*. a genetically determined shortness of vitamin K.

We published that DAH in coumarin users in many cases develop idiopathic pulmonary fibrosis (IPF) or nonspecific interstitial pneumonia (2,3). Coumarins, like warfarin are used as anticoagulant. They are generally called vitamin K antagonists because they block the recycling and thus regeneration of vitamin K via inhibition of vitamin K epoxide reductase 1 (VKORC1). The crucial role of vitamin K deficiency as a risk factor or even trigger for fibrosing interstitial pneumonias (IP), was further strengthened by our finding, that patients who used coumarins and had at least one episode of DAH were almost without exception carriers of a *VKORC1* or *CYP2C9* variant allele or both. VKORC1 is important in the recycling of vitamin K. A lower activity of VKORC1 results in a lower regeneration of vitamin K. Coumarins are metabolized by the iso-enzyme CYP2C9 into inactive metabolites. Lower activity of this iso-enzyme will lead to higher levels of the coumarins and thus to more inhibition of VKORC1 by these compounds (4). Low vitamin K activity leads to low coagulation and increases the chance for DAH. The catalytic role of iron in the hemorrhage results in oxidative stress, which is a critical factor in fibrotic processes (5). Relative vitamin K deficiency can cause various health problems, whereas controlled vitamin K supplementation is a well-tolerated treatment (4).

Moreover, we recently described a family with IPF who had *VKORC1* variant alleles in all of the family members who had IPF and had *CYP2C9* variants in all but one (6). Coumarins are not only drugs but are also found in the human diet. Many other xenobiotics are substrates or inhibitors of CYP2C9 and inhibit the breakdown of coumarins. The decreased VKORC1 in combination with decreased CYP2C9 activity thus elicits DAH symptoms (4) and hence IPF.

Although we realize more options are possible to explain the occurrence of DAH in various pathologies, the role of vitamin K deficit should be considered, as the clinical relevance is substantial.

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Correspondence: Marjolein Drent
ILD Center of Excellence, St. Antonius Hospital,
Nieuwegein, the Netherlands;
E-mail: m.drent@ildcare.nl

We recommend in case of unexplained DAH to genotype the patient and supplement with vitamin K when appropriate. Vitamin K supplementation is probably especially relevant for people who frequently have infections (and thus use antibiotics), use oral anticoagulants and/or come into contact with agents that affect coagulation, such as bacteria, fungi, cocaine and dyes.

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References

1. Alexandre AT, Vale A, Gomes T. Diffuse alveolar hemorrhage: how relevant is etiology? Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 47-52.
2. Wijnen PA, Verschakelen JA, Bast A, Bekers O, Drent M. Diffuse alveolar hemorrhage in coumarine users: a fibrosing interstitial pneumonia trigger? Lung 2013; 191 (1): 53-59.
3. Wijnen PA, Linssen CF, Haenen GRMM, Bekers O, Drent M. Variant VKORC1 and CYP2C9 alleles in patients with diffuse alveolar hemorrhage caused by oral anticoagulants. Mol Diagn Therap 2010; 14: 23-30.
4. Drent M, Wijnen PA, Bast A. Genetic polymorphisms and vitamin K deficiency: a risk factor or trigger for fibrosing interstitial pneumonias? Curr Opin Pulm Med 2018; 24 (3): 287-290.
5. Bast A, Weseler AR, Haenen GR, den Hartog GJ. Oxidative stress and antioxidants in interstitial lung disease. Curr Opin Pulm Med. 2010; 16 (5): 516-520.
6. Wijnen PA, Drent M, Bekers O, Verschakelen J, Bast A. VKORC1 and CYP2C9 polymorphisms: A case report in a Dutch family with pulmonary fibrosis. Int J Mol Sci 2019; 20 (5): 1160.