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Balkan Endemic Nephropathy – Still continuing enigma, risk assessment and underestimated hazard of joint mycotoxin exposure of animals or humans

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ABSTRACT

The spreading of mycotoxic nephropathy in animals/humans was studied. The possible etiological causes provoking this nephropathy were carefully reviewed and analyzed. The natural content of the most frequent nephrotoxic mycotoxins in target feedstuffs/foods were investigated, in addition to their significance for development of renal damages in endemic areas. An estimation of the level of exposure of humans to the nephrotoxic mycotoxin, ochratoxin A (OTA), is made. The possible synergism or additive effects between some target mycotoxins in the development of nephropathy is also covered. The significance of joint mycotoxin interaction and masked mycotoxins, in addition to some newly isolated fungal toxic agents in the complicated etiology of mycotoxic nephropathy ranged in Balkan countries is discussed. The importance of some target fungal species which can induce kidney damages was evaluated. The morphological/ultrastructural, functional and toxicological similarities between human and animal nephropathy are studied. The possible hazard of low content of combinations of some target mycotoxins in food or feedstuff ingested by pigs, chickens or humans under natural conditions is evaluated and a risk assessment was made. Some different but more effective manners of prophylaxis and/or prevention against OTA contamination of feedstuffs/foods are suggested. A survey was made in regard to the best possible ways of veterinary hygiene control of OTA-exposed animals at slaughter time for preventing the entrance of OTA in commercial feedstuffs/food channels with a view to reduce the possible health hazard for humans. The economic efficacy and applicability of such preventive measures is additionally discussed and some practical suggestions are made.

Contents

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1. Introduction

Balkan Endemic Nephropathy (BEN) is a chronic renal disease encountered in some rural populations in Bulgaria, Romania and ex-Yugoslavia, which has been observed mainly in farmers aged between 30 and 50 years. The disease has a strict endemic and family character, scarce clinical features, a subtle onset and a bad prognosis. It usually progresses in a slow way and can be noticed just when the majority of nephrons are already damaged [1]. Currently, there is an expert agreement that the disease has unknown etiology, although there are some opinions that mycotoxins and/or aristolochic acid (AA) are probably involved in it [2–11]. On the other hand, mycotoxic porcine/chicken nephropathy (MPN/MCN), encountered in the same endemic areas, was recently seen to possess a different and much complicated pathology and etiology being mainly provoked by alimentary ingestion of some target mycotoxins such as ochratoxin A (OTA), fumonisin B_1 (FB_1), citrinin (CIT), penicillic acid (PA), in addition to not yet identified metabolite (UM) or deoxynivalenol (DON), having a common synergistic, additive or less than additive interaction [7,12–14] (Table 1).

Until now, only OTA and partially CIT were etiologically associated with spontaneous mycotoxic nephropathy (MN) in animals/chicks [15] as based on many spontaneous or experimental studies and OTA was concluded to be the main etiological agent of porcine/chicken nephropathy in Denmark and Sweden [16,17] and subsequently in all over the world. Recently, this assumption was however contradicted by some experimental [18–20] and spontaneous studies in different countries [12,21] (Fig. 1). In these countries spontaneous nephropathy in pigs [22–24] or chicks [25] established previously, was recently found to be provoked by low contamination levels of several nephrotoxic mycotoxins such as OTA, PA, FB_1, CIT and/or DON (Table 1) [12,21], which were found to have a strong synergistic and/or additive interaction as shown in series of experimental *in vivo* [18–20,26–37] or *in vitro* [37–42] studies. This synergistic and/or additive interaction usually enhances the toxic effect on kidney and also increases the known immunosuppressive effects of the same mycotoxins [43] (Table 1).

MPN/MCN is appeared to be a problematic disease in the countries with powerful stock-breeding such as Denmark. The disease has however some differences in the way of manifestation, especially in regards to its clinicomorphological picture, which often is influenced by different combinations of mycotoxins involved or by some secondary bacterial infections appearing as a consequence of the strong immunosuppressive effects of the same target mycotoxins provoking this nephropathy [44]. Therefore, the target purpose of this review is to contribute further to a better explanation of some variations in clinicomorphological picture in animals/chicks or humans with spontaneous MN or BEN and to clarify the different etiological nature of some spontaneous cases of MN in various countries having different pathological findings.

2. Epidemiology and the main endemic features of MPN/MCN/BEN

As a rule, MPN is seen in certain pig farms and reached the largest dissemination following wet years [22] similarly to BEN [5,14]. The farms having MPN/MCN usually had a record of inappropriate feedstuffs storage, but in some cases the source of the problem derived from the grain of target feed plants collected during moist or rainy time without a proper drying and/or storage. As a consequence, all farms using these plants for feedstufs supply

Fig. 1. Mottled appearance of kidney of pig of 6–8 month-age with spontaneous MPN identified at the slaughterhouse in Bulgaria.

Table 1
Concentration of various nephrotoxic mycotoxins in feed/serum/urine samples from pig farms in Bulgaria having nephropathy problems such as enlarged and mottled or pale appearance of kidneys at slaughter time and isolated producing fungi [12].

Mycotoxin	Years	Blood/Urine or Feed	Number of samples	Range of % of positive	Range of mean levels μg/kg(L) (ppb)
OTA	2006–2007	Feed	50	100	188.8–376.4
		Blood	20	80–90	6.3–28.8
		Urine	20	100	3.5–6.2
PA	2006–2007	Feed	50	88–92	838.6–904.9
		Blood	20	80–90	22.9–23.3
		Urine	20	60	1.6–1.7
CIT	2006–2007	Feed	50	92–96	54.7–120.5
		Blood	20	70–80	1.3–1.6
		Urine	20	100	1.7–1.8
DON	2006–2007	Feed	50	60–100	51.4–72.7
		Blood	20	0–10	0–7.6
		Urine	20	0–10	0–5.1
FB1	2006–2007	Feed	50	92–96	3254–5564