Immigrant status in an endemic area is a negative predictor for proximal tubule damage in endemic (Balkan) nephropathy

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Objectives:

Endemic nephropathy (EN) represents a form of **aristolochic acid nephropathy (AAN)** where AA was ingested **via contaminated bread**. A study performed on Ukrainian immigrants – “Ukraine has no cases of EN” - who settled in Croatia in the early 20th century provided the first solid evidence of an environmental etiology of disease - Ukrainian settlers in endemic areas had similar risks of developing EN as native Croats while those who settled in non-endemic areas were not at increased risk for EN. In recent decades, improved harvesting and milling technology has essentially eliminated the contamination of wheat grain with Aristolochia seeds. Recent emigration from non-endemic areas of Bosnia (presumably not exposed to AA) into Croatian endemic area provided the opportunity to test the hypothesis that exposure to this environmental toxin in endemic area is reduced or no longer present. We hypothesize, **that immigrants from Bosnia (BoEN), who settled in an endemic area in Croatia 15 to 30 years ago, would be at a lower risk of developing EN because of reduced exposure to AA.** To test this hypothesis we analyzed an early hallmark of EN, proximal tubule damage (PTD), and renal function in BoEN immigrants and long-term residents of Croatian endemic and non-endemic villages.

Methods and subjects:

This cross sectional study conducted from 2005 till 2010 encompassed 2161 farmers, divided into three groups: indigenous inhabitants of EN and non-EN villages, and Bosnian immigrants in whom parameter of proximal tubule damage (PTD) and the prevalence of chronic kidney disease (CKD) were analysed. After signing informed consent, participants completed an extensive survey regarding past and present exposure to AA and provided a spot urine and fasting blood sample. Alfa-1 microglobulin to creatinine ratios (α1/CR) higher than 31.5 mg/g and eGFR lower than 60 ml/min were considered pathological.

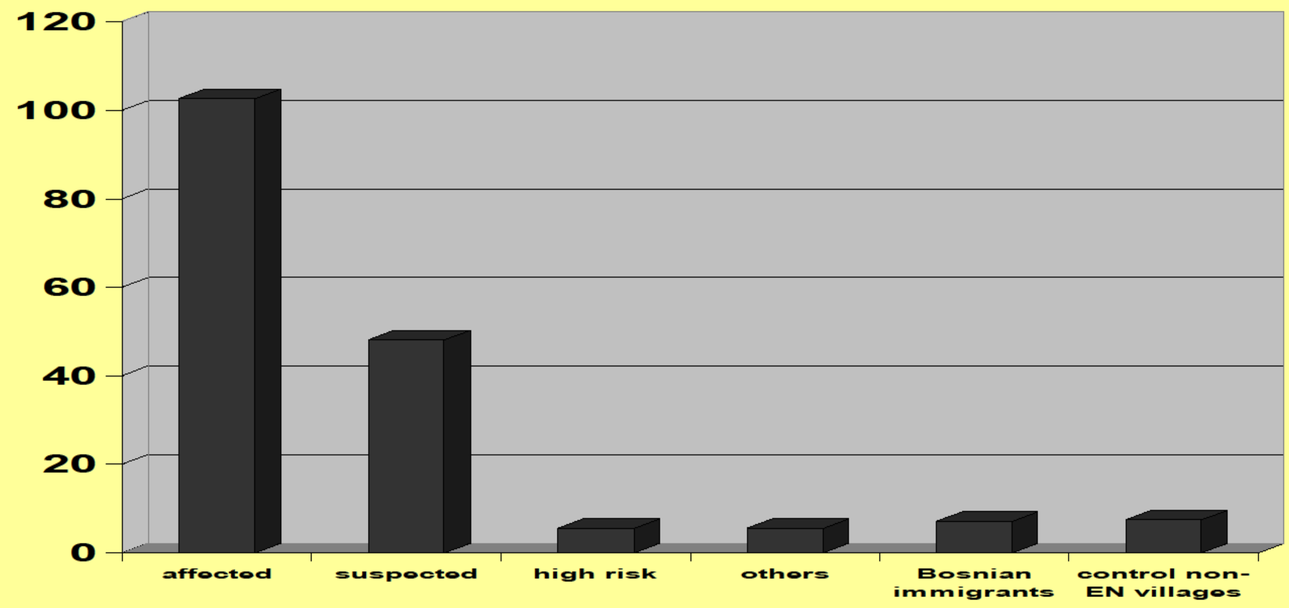
	Group	Settled	Diseased/ Affected	Suspected EN	High risk for EN	Others
Villages		(years)	N (%)	N (%)	N (%)	N (%)
Endemic	Autochthonous		30 (1.8)	119 (7.1)	553 (32.8)	985 (58.4)
	Bosnian immigrants	15 – 30	0	1 (1)	2 (2)	99 (97.1)
Control non-endemic	Autochthonous		0	0	4 (1.07)	368 (98.9)
	Bosnian immigrants		0	0	1 (2.5)	39 (97.5)

Results:

	Endemic Villages	Control non-endemic villages	Bosnian immigrants	P
α-1CR (mg/g)	5.98 (3.75-10.53)	7.39 (4.74-12.47) *	7.04 (4.66-11.17)	<0.001
ACR (mg/g)	5.29 (3.51-10.68)	5.68 (3.87-10.61)	5.58 (3.95-9.64)	0.298
Serum creatinine (μmol/L)	83 (74-95) †	80 (72-92)	75 (68.8-85.3) *,†	<0.001
eGFR (ml/min/1.73m²)	80 (67-94)	81 (70-92)	88 (73-100) *,†	0.003
Hemoglobin (g/L)	137 (129-147)	140 (130-148)	138 (130-147)	0.128
Urine specific gravity	1,015 (1,010-1,021)	1,015 (1,010-1,020)	1,016 (1,011-1,022)	0.219
Left kidney length (mm)	109 (100-117)	113 (108-119)*	112 (103-120)	<0.001
Right kidney length (mm)	109 (101-117)	114 (106-120)*	114 (102-118)	<0.001
α-1CR >31.5mg/g N(%)	82 (7.3)	10 (0.3)	1 (1.3)	0.003
ACR >30mg/g N(%)	189 (15.8)	38 (11.4)	7 (6.7)	0.049
eGFR <60ml/min N(%)	280 (16.6)	34 (9.2)	7 (6.7)	>0.001

*significant difference (p<0.05) with the endemic villages group ; † significant difference (p<0.05) with the control non – endemic villages group; ‡ significant difference (p<0.05) with the Bosnian immigrants group

Baseline characteristics were similar in terms of age, gender, body mass index, blood pressure, and the prevalence of hypertension and diabetes. We found similar degrees of albuminuria, as detected by the albumin to creatinine ratio (ACR), hemoglobin levels, and urine specific gravity among all three subgroups (all with p>0.05). Estimated glomerular filtration rate (eGFR) was higher among Bosnian immigrants than in the two indigenous groups (p=0.003), while the shortest kidneys were found in subjects living in endemic villages (p<0.001). More farmers with biomarkers of kidney function above cut off values resided in endemic villages compared with those in non-endemic villages and Bosnian immigrants. Regarding α-1CR, 7.3% of villagers from endemic area had values above the cut off value (>31.5 mg/g), compared with 0.3% of controls and 1.3% of immigrants (p=0.003). Further, 16.6% of natives from endemic villages had eGFR values below the cut off value (<60 mL/min1.73 m2), as compared with 9.2% of the natives from non-endemic villages and 6.7% of the Bosnian immigrants (p<0.001). **Rates were comparable between Bosnian immigrants, natives from non-endemic villages, and unaffected subjects from endemic villages.**



α-1 microglobulinuria to creatinine ratio (α-1CR) was higher in 'affected' and 'suspected' cases than in 'high-risk' cases, controls and Bosnian immigrants (p<0.001) (figure 1).

No EN case was detected in immigrants.

Immigrant status was found to be **independent negative predictor of PTD** (OR 0.35; 95%CI 0.14-0.86;p=0.022),

unlike positive family history for EN which was strongly positive predictor

(OR 2.31;95%CI 1.43-3.74;0.001).

Twenty years ago BoEN observed significantly less A.clematitis in farming fields, less Aristolochia seeds among wheat seeds, and less frequently baked bread from their own flour compared to CroEN subjects (all p<0.001).

Conclusions: Bosnian immigrants and autochthonous Croats residing in an endemic area are significantly less exposed to dietary AA than they were 30 years ago. Proximal tubule damage was not more frequently presented in endemic than non-endemic villages. No EN cases were detected in Bosnian immigrants. We predict that the prevalence of disease will continue to decrease over time

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H) Clinical Nephrology, CKD. H1) Lab methods, progression & risk factors for CKD 1-5, nutrition in CKD, renal diseases (except GNs and cystic diseases).
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