ACTIVIN A IN CARCINOID HEART DISEASE: A POSSIBLE ROLE IN DIAGNOSIS AND PATHOGENESIS

Deidi Strickland Bergestuen, Thor Edvardsen, Svend Aakhus, Thor Ueland, Erik Øie, Morten Vatn, Pål Aukrust, Espen Thiis-Evensen

Oslo University Hospital, Rikshospitalet, Oslo, Norway

BACKGROUND AND AIM

Carcinoid heart disease (CHD), a known complication of neuroendocrine tumors (NET), is characterized by right heart fibrotic lesions. Though serotonin is likely involved, the pathogenesis of CHD remains unclear. Cytokines and growth factors with fibrogenic properties may play a role. We sought to examine the relationship between plasma levels of fibrogenic cytokines and growth factors and CHD, to provide further insight into possible biomarkers of CHD and into the pathogenesis of CHD.

METHODS

Plasma samples from 71 NET patients (small intestine = 69, appendix = 1, proximal colon = 1) and 18 controls were analyzed using enzyme immunoassays. All patients underwent echocardiography. CHD was defined as more than mild right-sided valvular regurgitation and/or any valvular stenosis plus pathological valvular morphology. Early stage CHD was defined as either mild-to-moderate or moderate valvular dysfunction. Advanced CHD was defined as moderate-to-severe or severe valvular dysfunction. In addition, a scoring system for CHD previously described by Denney, et al was applied (CHD score = #points/total possible (14) x 100). Tumor biopsies and a CHD lesion were analyzed via immunohistochemistry.

RESULTS

Demographics

15 patients had CHD, 10 with early stage CHD (median score 46%) and 5 with advanced CHD (median score 64%). Advanced stage CHD patients had a significantly higher CHD score (p=0.005). CHD patients were older (p=0.01), had larger (p=0.007) and more numerous liver metastases (p=0.04), and had elevated 24-hour U-5HIAA (p=0.03) and serum chromogranin A levels (p=0.02).

Characteristic	CHD (n=15)	No CHD (n=56)	P-value
Gender (%M/F)	53/47	48/52	0.78
Age†	72 (50-83)	63 (33-76)	0.01
Carcinoid syndrome	100%	82%	0.11
Duration of illness (yrs)	5 (2-8)	4 (1-6)	0.38
Som analog tx (mos)	26 (13-83)	24 (8-47)	0.88
U-5HIAA‡	20 (6-47)	6 (2-25)	0.03
CgA§	26 (15-153)	16 (6-37)	0.03
% with liver mets	93%	86%	0.67
No. of liver mets	15 (6-20)	7 (1-13)	0.04
Size liver mets (mm)	19 (18-28)	14 (9-19)	0.007

*Results are given as median (interquartile range) unless otherwise specified. †Median (range).‡µmol/mmol Cr. §nmol/ml

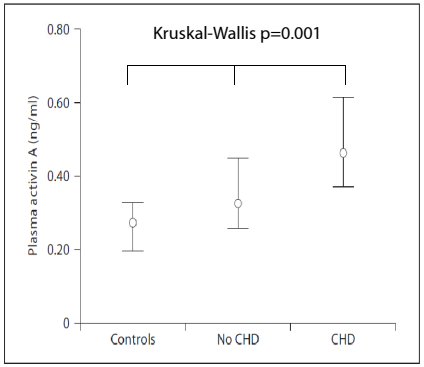
Markers of fibrosis

CHD patients had higher plasma levels of C-reactive protein (CRP), osteoprotegerin (OPG) and activin A (Act A) than patients without CHD. A direct correlation between activin A and U-5HIAA levels was observed in the total patient group (r=0.30, p=0.02).

Marker	CHD	No CHD	P-value
CRP (mg/L)	1.71 (0.50-7.49)	0.70 (0.31-1.65)	p=0.01
OPG (ng/ml)	5.58 (3.71-7.02)	3.85 (2.95-5.06)	p=0.005
Activin A (ng/ml)	0.46 (0.37-0.61)	0.33 (0.25-0.45)	p=0.005

Activin A in relation to CHD

High-low-close graph demonstrating the relationship between plasma activin A levels and the presence of CHD. Activin A levels were elevated to the same degree in both early and advanced CHD (0.48 vs. 0.46 ng/ml, p=0.40). Activin A ≥0.34 ng/ml detected CHD with 87% sensitivity and 57% specificity.



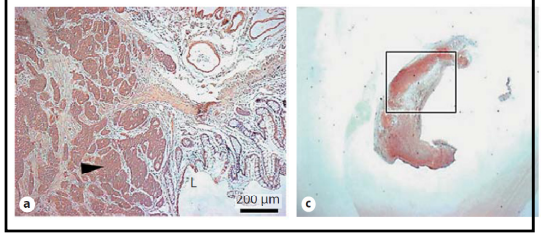
Independent predictors of CHD*

	Univariate OR	Multivariate OR
Act A ≥0.34 ng/ml	8.67 [1.78;42.08]	5.35 [1.01;28.17]
Age ≥69.5	9.20 [2.57;32.85]	6.10 [1.60;23.24]
OPG ≥5.30 ng/ml	6.90 [2.00;23.82]	

*Logistic regression

Immunohistochemistry

Tumor tissue from a small intestinal NET and a CHD lesion showing positive staining for activin A.



CONCLUSION

Elevated plasma activin A levels are associated with the presence of CHD. Activin A is expressed in tumor tissue and in CHD lesions.