The incidence of consecutive manifestations of Von Hippel-Lindau disease

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ECE2015 16-20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY

Background

Von Hippel Lindau (VHL) disease is a rare tumor syndrome with a high penetrance.

VHL patients develop numerous disease related manifestations in multiple organs during life, but the difference in growth velocity and incidence of lesions in different organs in the individual VHL patient, is still not precisely defined.

Aim

To gain insight in the incidence of consecutive new disease manifestations in the organs of patients with VHL.

Methods

Clinical data including the age at diagnosis of each new VHL-related manifestation of 75 VHL (37 male, 38 female) patients (type 1 and 2a/b) with standardized follow-up in two VHL-expertise centers in the Netherlands were retrospectively evaluated.

Only consecutive lesions in the retina, the central nervous system, the kidneys and the pancreas were analyzed.

New organ lesions were defined as a new organ manifestations detected with imaging or in case of retinal lesions detected by fundoscopy.

The Kaplan Meier method was used to construct the cumulative proportions of first and all consecutive manifestations in each organ against age.

The cumulative average number of manifestations in all organs during life was calculated by summating these cumulative proportions.

Poisson model parameters were used to calculate average time to the detection of VHL manifestations in each organ as described previously.
Kruizinga et al. Endocr. Relat. Cancer, 2014

Characteristic Mutation	No.(%)	VHL- type	Mean age (years) at last FU with range	VHL-related manifestations
c.208G>A	1 (1%)	1	20	HBr
c.-213- ?_463+?del	4 (5%)	1	45 (38-48)	HBr, HBc, HBsc, RCC, PNET, Cr, Cp
c.241C>T	2 (3%)	2a/b	47 (34-59)	HBr, HBc,HBsc, RCC, PNET, Pheo, Cr
c.259_260-insA	1 (1%)	1	42	HBr, HBc,HBsc, RCC, Cr, Cp
c.277G>A	2 (3%)	2a/b	48 (35-60)	HBr, HBsc, Pheo, Cr, Cp
c89c297+	25 (33%)	1	40 (17-70)	HBr, HBc,HBsc, RCC, PNET, Cr, Cp
c.340+1G>A	1 (1%)	1	32	HBr, HBc, HBsc, RCC, Cr, Cp
c.341-59_341-14del	2 (3%)	2a/b	52 (33-67)	HBr, HBc, RCC, Pheo, Cr, Cp
c.358A>G	1 (1%)	1	15	HBsc
c.407T>C	1 (1%)	1	41	HBc, HBsc, RCC, Cr, Cp
c.462A>C	1 (1%)	2a/b	71	HBc, Pheo. Cr
c.497T>C	1 (1%)	2a/b	27	PNET, Pheo
c.499C>T	1 (1%)	2a/b	43	HBr, HBsc, RCC, Pheo, Cr
c.500G>A	11 (15%)	2a/b	45 (21-65)	HBr, HBc,HBsc, RCC,pNET, Pheo, Cr, Cp
c.509T>A	15 (20%)	2a/b	45 (16-71)	HBr, HBc,HBsc, RCC, pNET, Pheo, Cr, Cp
c.565delG	1 (1%)	1	30	HBc, Cr
c.573+2T>C	1 (1%)	1	31	HBr, HBc, HBsc, RCC, Cr
235 (CAG-TAG)	1 (1%)	1	63	HBr, HBc, HBsc, RCC, Cr
Rearrangement SB	1 (1%)	1	25	HBr, HBc, HBsc, Cr, Cp
Unknown	1 (1%)	1	44	HBr, HBc, HBsc, RCC, Cr, Cp
Nothing found	1 (1%)	1	40	HBr, HBc, Cr

SB, Southern blot; HBr, retinal hemangioblastoma; HBc, cerebellar hemangioblastoma; HBsc, spinal cord hemangioblastoma; RCC, renal cell cancer; pNET, pancreatic neuroendocrine tumor; Pheo, pheochromocytoma; Cr, renal cyst; Cp, pancreatic cyst; FU, follow up.

Table 1. Characteristics of the VHL patients

Results

Consecutive VHL-related kidney and retina manifestations during life occur according to Poisson distribution model.

The second VHL pancreas manifestation occurred later and the consecutive CNS hemangioblastomas were detected earlier than predicted by the Poisson model.

The average total systemic number of manifestations rises in a linear way to 7 VHL-related manifestations at age 60 years.

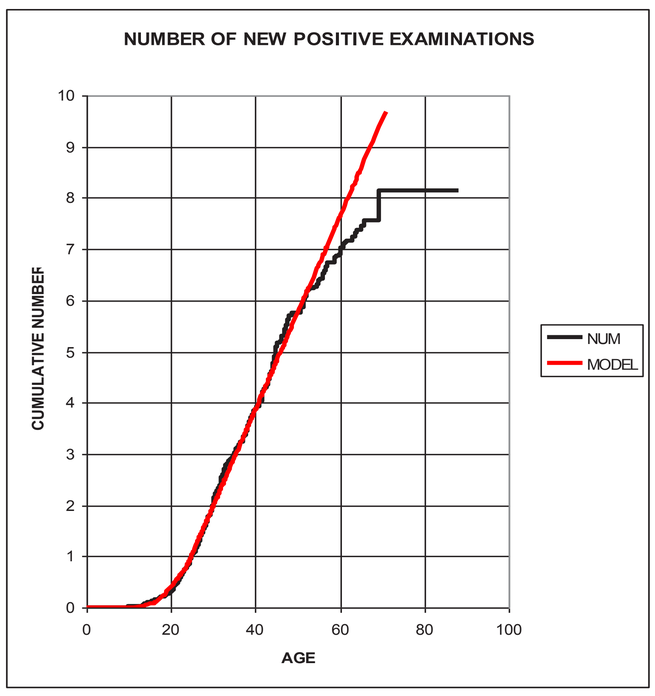

Figure 2. Cumulative number of VHL-related manifestation during life per VHL patients summated for all organs
red =calculated, black= observed

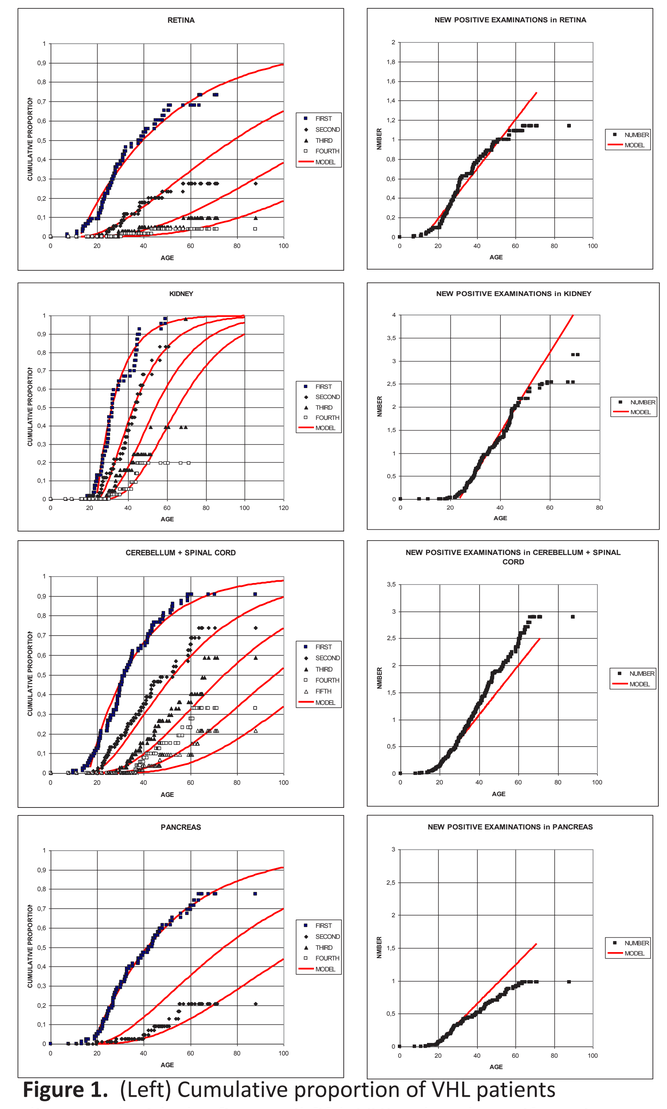

Figure 1. (Left) Cumulative proportion of VHL patients diagnosed with the first until fifth VHL-related manifestation during life ; (Right) mean number of organ manifestations during life per VHL patient.
red =calculated, black= observed

Comments

The discrepancy in predicted and observed incidence in CNS and pancreas manifestation are in contrast with the results of the retina and kidney manifestations, but can be explained by the limitations in the detection of pancreas lesions and the presence of incomplete surgery of the CNS lesions resulting recurrence of the same lesion.

The increase in predicted and observed cumulative average number of all manifestations is shown in Figure 2. The increase is strikingly linear and as predicted during life until age 60 years, after this age the predictions were slightly higher than the number of VHL-related manifestations reported. At age 60 years the mean number of manifestations diagnosed per VHL patient was 7.

Conclusions

The incidence of new VHL-related manifestations after the first organ involvement is highly constant during life in VHL patients.

Therefore, the accelerations and arrests in appearance of new manifestations that can be observed in individual subjects are caused by the randomness of events and not by variation in disease activity.

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17 ECE 6-GP-29
Endocrine tumours
Thera Links
DOI: 10.3252/pso.eu.17ece.2015
Poster presented at: ECE2015 16-20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY
PosterSessionOnline.com