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Serum Vanillylmandelic Acid/Homovanillic Acid Contributes to Prognosis Estimation in Patients with Localised but not with Metastatic Neuroblastoma

F. Berthold, D.H. Hunneman, D. Harms, H. Käser and J. Zieschang

In 211 patients with neuroblastoma, serum vanillylmandelic acid (VMA) and homovanillic acid (HVA) levels were determined and correlated to stage, histological differentiation, ferritin, neuron-specific enolase, lactate dehydrogenase (LDH) and outcome. Elevated serum VMA and/or HVA levels were found 16% less frequently than elevated urine levels. The incidence of the elevated serum levels increased with stage (stages I–III 58%, IV 78%, IVS 100%). Increased VMA/HVA ratios were not associated with a higher grade of tumour differentiation. Serum ferritin and neuron-specific enolase showed no correlation, and LDH a borderline non-random correlation with the serum catecholamine metabolites. Using age-related reference values a quotient of serum VMA/HVA ($P = 0.061$)< 0.7 indicated a poorer event-free survival (48 ± 10%) than ratios ≥ 0.7 (event-free survival 81 ± 6%) for children with localised neuroblastoma ($P = 0.0004$). No correlation with prognosis was detected for patients with stage IV and stage IVS disease. We conclude that serum VMA and HVA determinations may be useful as tumour markers for 71% of neuroblastoma patients, and aid in estimating the prognosis in children with localised disease.
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INTRODUCTION

THE DETERMINATION of the two major catecholamine metabolites vanillylmandelic acid (VMA) and homovanillic acid (HVA) in urine has been widely recognised as a valuable tool for diagnosis and response evaluation [1–5] as well as a tumour marker for possible early detection in a mass screening programme [6, 7]. The degree of biochemical tumour maturation indicated by the VMA/HVA ratio in urine has been thought to show prognostic information when comparing those data with histological differentiation patterns [8–11], DNA ploidy [12] and N-*myc* amplification [13, 14]. Recently serum determinations of VMA and HVA have become available [15, 16], considerably facilitating disease monitoring because of their independence of 24 h urine collection. Here we report the prognostic impact of initial serum VMA and HVA levels in 211 neuroblastoma patients and their relationship to other prognostic factors.

PATIENTS AND METHODS

Serum samples of 211 neuroblastoma patients were obtained for VMA and HVA determinations at diagnosis. 97 children had localised disease (stages I–III according to Evans), 93 patients metastatic neuroblastoma (stage IV) and 21 infants stage IVS. The 211 patients with known serum VMA and HVA values were compared with 357 patients of the same trial in whom those data were not available (total 568 patients). We found no differences with respect to stage, age at diagnosis, incidences of abnormal lactate dehydrogenase (LDH) and ferritin levels, surgical resectability, histological grade and survival parameters [event-free survival (EFS), survival (S)], indicating that the group investigated here was representative of the total group. The children were treated according to the German cooperative trials NB 82 and NB 85 [17]. No differences in EFS were

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Table 1. Comparison of serum and urinary catecholamine metabolites in 211 patients with neuroblastoma

Evans' stage	Patients per stage	Abnormal serum VMA, HVA: VMA (*n*)	HVA (*n*)	VMA + HVA (*n*)	VMA and/or HVA (*n*)	VMA and/or HVA (%)	Abnormal urinary catecholamine metabolites (%)
I–III	97	38	46	28	56	57.7	78.6
IV	93	62	71	60	73	78.5	92.8
IVS	21	20	16	15	21	100.0	100.0
Total	211	120	133	103	150	71.0	87.2

observed between the two trials [18], allowing the inclusion of patients from both for prognostic evaluation.

The VMA and HVA levels were determined by mass fragmentography as described earlier [15]. Because of considerable changes in normal values with age [16] the results are expressed as the ratio of the determined value related to the upper normal limit, which is defined as the mean + 2 standard deviations. Values ≤ 1.0 were considered normal and borderline, values above 1.0 as pathological. The VMA/HVA ratio is defined by the upper normal limit-ratio VMA/upper normal limit-ratio HVA. Urinary catecholamine metabolite determinations were performed by HPLC, including VMA and HVA in all cases and further metabolites (dopamine, normetanephrine, 3-methoxytyramine and others) in selected cases.

Panel-reviewed histological grading of untreated tumour tissue was possible in 122 patients (66 patients of stages I–III, 44 of stage IV and 12 of stage IVS). Inclusion of patients with preoperative chemotherapy increased the number with histologic grading to 165 (stages I–III, 81 patients; stage IV, 67 patients, stage IVS, 17 patients). The modified Hughes' system was used [19], which classifies the tumours by differentiation patterns. In brief, grade 3 represents undifferentiated neuroblastoma, grade 2 contains cell elements with partial and grade 1 with full ganglionic differentiation in addition to areas of more or less undifferentiated neuroblastic tissue (ganglioneuroblastoma).

The prognosis refers to EFS. Recurrence, tumour progression or death were counted as events. Statistical analysis and Kaplan–Meier EFS estimates were performed on an IBM Personal System/2 Model 60 using the SAS statistical package 88.2 and BMDP2L.

RESULTS

The frequency of abnormal serum catecholamine metabolite levels at diagnosis appeared to be stage-dependent (Table 1). HVA was more frequently elevated than VMA (63.0% vs. 56.9%). At least one abnormal marker was found in 71% of cases, while both showed increased levels in 48.8%. VMA and/or HVA showed abnormal values in localised neuroblastoma less frequently than in metastatic neuroblastoma. Urinary catecholamines including other metabolites than HVA and VMA showed abnormal levels in 16% more patients than using HVA and VMA in serum alone.

For analysis of VMA/HVA ratios all patients with abnormal and normal marker levels were included. The group with normal VMA and HVA did not show any particular pattern using a multitude of criteria (distribution, age, stage, prognosis). Figure 1 demonstrates the distribution of VMA/HVA ratios according to stage. The VMA/HVA quotient was higher in localised disease [median 1.18; interquantile range (IQR) 0.59–1.91] compared with metastatic neuroblastoma (0.81, 0.57–1.61). The highest VMA/HVA ratios were observed in infants with stage IVS (2.87, 1.50–4.71). Elevated catecholamine levels and VMA/HVA ratios > 0.7 were found in 5/18 (28%) stage I, in 4/12 (33%) stage II and in 25/67 (37%) stage III patients.

EFS was not different for patients with normal compared with abnormal serum VMA and/or HVA if analysed on a stage-related basis. The same result was obtained using elevated vs. normal catecholamine metabolite excretion in the urine. On the other hand the serum VMA/HVA ratio showed a significant prognostic influence on patients with localised neuroblastoma (Fig. 2). The most discriminating value was 0.7, resulting in an 81% EFS for patients with VMA/HVA ≥ 0.7 compared to 48% EFS for children with VMA/HVA < 0.7 (logrank test 12.36, $P = 0.0004$). In patients with metastatic neuroblastoma (stages IV, IVS) there was no influence of various VMA/HVA ratios on EFS ratio and time. The best discriminating VMA/HVA quotients appeared to be the ratios 0.80 for stage IV (logrank test 2.556, $P = 0.1099$, n.s.) and 4.00 for stage IVS (logrank test 1.621, $P = 0.2030$, n.s.).

High VMA/HVA ratios are considered to represent a more mature biochemical pattern of the tumour [8–11]. Therefore we investigated their relationship to the histologic grade of differentiation. Table 2 shows the distribution of grades according to stage demonstrating an increased frequency of immature neuroblastoma with advancing stage. Grade 3 tumour represented one-third (32%) of localised, but more than half (57%) of metastasised tumours. The most immature features were seen in infants with stage IVS. These figures obtained only from untreated patients with known serum VMA, and HVA levels were identical to those obtained from the total trial NB 82 and NB 85 group. If the patients with preoperative chemotherapy were included the incidence of more differentiated neuroblastoma (grade 1) increased, reflecting the predominant activity of cytostatic drugs on the immature part of the tumour. However, only the untreated samples were included in further analysis.

The most differentiated grade 1 was present in 7 out of 13 stage I–III patients (54%) with a VMA/HVA ratio less than 0.7, but only in 9 out of 53 patients (17%) with a VMA/HVA ≥ 0.7. This pattern is surprising because this appears to reflect an association of differentiated histology with undifferentiated biochemistry ($\chi^2 = 7.73$, $P = 0.005$), although the limited number of patients analysed warrants a cautious interpretation. However, the particularly high VMA/HVA ratios in IVS patients (Fig. 1) and their low grade of histological differentiation (Table

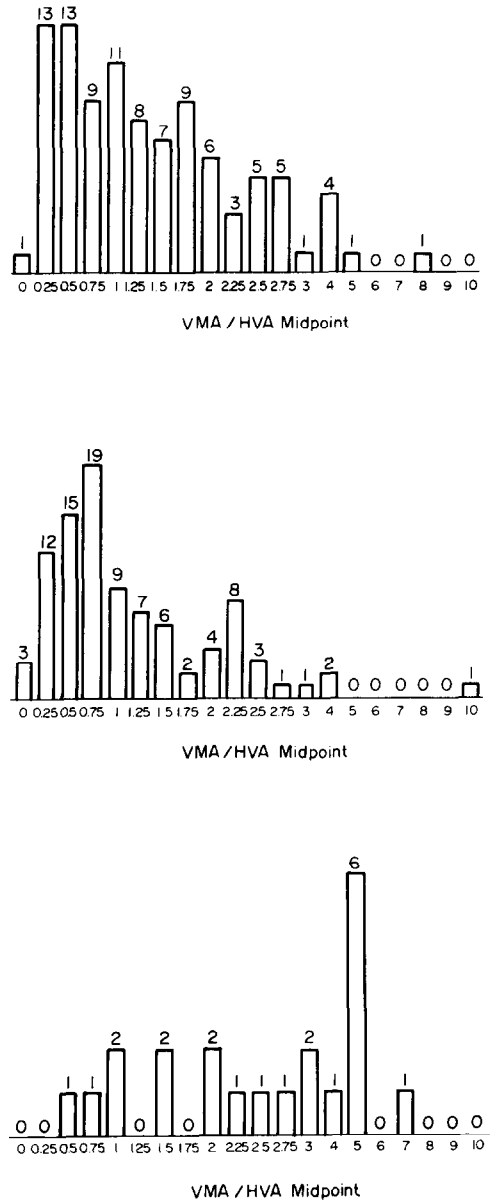

Fig. 1. Distribution pattern of the ratios VMA/HVA in 211 neuroblastoma patients. Upper panel stages I–III (n = 97); intermediate panel stage IV (n = 93); lower panel stage IVS (n = 21).

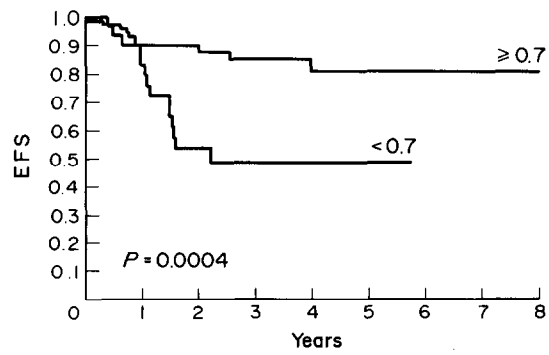

Fig. 2. EFS in 97 patients with neuroblastoma stages I–III by VMA/HVA ratios. NB 82/85. < 0.7 29 patients (14 events): EFS [mean (S.D.)] 0.48 (0.10); ≥ 0.7 68 patients (10 events): EFS 0.81 (0.06).

Table 2. Distribution of histological grades (Hughes) in neuroblastoma patients

	Evans' stage			
	I–III n = 66 (77)*	IV 44 (67)	IVS 12 (17)	Total 122 (165)
Hughes' grade	(%)	(%)	(%)	(%)
1	24 (30)	20 (33)	8 (12)	21 (29)
2	44 (41)	23 (21)	25 (29)	34 (32)
3	32 (30)	57 (46)	67 (59)	44 (39)
Totals	100 (101)	100 (100)	100 (100)	99 (100)

* Numbers refer to samples obtained by first-look surgery (before chemotherapy), numbers in parentheses refer to samples obtained by first-look *and* delayed first-look surgery (before and during chemotherapy).

2) point in the same direction. The known prognostic advantage (EFS ratios and time) of patients with more mature histology [20] and a higher VMA/HVA ratio (Fig. 2) was maintained looking at the subgroups with VMA/HVA < 0.7 and VMA/HVA ≥ 0.7, albeit with only a statistical trend due to small numbers. No association of the VMA/HVA quotient to neuron-specific enolase in serum was seen (n = 64, P = 0.303) or to ferritin (n = 74, P = 0.716). The correlation of VMA/HVA < 0.7 with abnormal serum LDH was in the borderline range (n = 89, χ^2 = 3.500, P = 0.061).

DISCUSSION

The association of an immature catecholamine metabolite excretion pattern in urine and a poorer prognosis has been reported earlier [8–10]. This has been attributed to the enzymatic capacity of the tumour tissue. VMA represents the end product of the adrenaline and noradrenaline metabolism. Deficiencies of major catabolic enzymes, e.g. dopamine-β-hydroxylase, results in a pathway switch at the level of dopamine with HVA as end product. Gitlow *et al.* [8] observed in 54 children with neuroblastoma of all stages that higher HVA levels were associated with poorer survival. A significant correlation to histological neuroblast differentiation could not be found [8, 11]. Laug *et al.* [9] introduced the VMA/HVA ratio as a simple measurement of biochemical tumour differentiation and detected in 34 stage IV patients that a lower VMA/HVA ratio indicated a poorer prognosis. This finding was supported by La Brosse *et al.* [10], who demonstrated in 147 stage IV patients a significantly better 2-year survival for children with higher VMA/HVA ratios. According to Graham-Pole *et al.* [11] the urinary catecholamine excretion pattern differed often markedly from the tumour catecholamine pattern in the same child, and no correlation with the degree of histological differentiation was observed. Abramowsky *et al.* [12] studied the DNA ploidy pattern by flow cytometry in 39 patients and found that non-aneuploid tumours secreted higher levels of the early pathway catecholamine metabolites DOPA, dopamine and HVA, and were more likely to come from stage III and IV patients. Nakagawara *et al.* [14] reported from 32 patients with stage III and IV neuroblastoma a favourable prognostic impact of the noradrenaline/dopamine ratio in urine and tumour tissue, but not of the VMA/HVA ratio. Higher noradrenaline/dopamine ratios were associated with non-amplified N-*myc* (1–10 copies). In another study [21]

30 neuroblastoma patients found by mass screening had a VMA/HVA ratio of 0.95 (0.40), favourable stages I–III and no N-*myc* amplification. In 13 mass screening negative, but later neuroblastoma-presenting, children the VMA/HVA ratio depended on the N-*myc* status. 6 patients without N-*myc* amplification showed a VMA/HVA ratio of 1.17 (0.70), while the 7 with N-*myc* amplification demonstrated a significantly lower quotient of 0.33 (0.16). All these data suggest a poor prognostic influence of immature urinary catecholamine patterns [8–10, 12, 14, 21], which does not exhibit a clear correlation to the histological differentiation patterns [8, 11], but with an association to non-aneuploid tumours and N-*myc* amplification [13, 14, 21].

This is the first study correlating serum VMA and HVA with prognosis in neuroblastoma patients obviating the necessity of a 24 h urine collection in small children. The use of values expressed as the 'multiples of the upper normal reference limit' made them very well comparable through the various ages. In this way a clear stage dependence was found for the incidence of increased values and the VMA/HVA ratio. In stage I–III neuroblastoma abnormal catecholamines were detected less frequently (58%) and the VMA/HVA ratio was higher (1.18) compared with stage IV neuroblastoma (78% and VMA/HVA 0.81). All infants with stage IVS disease demonstrated abnormal catecholamine metabolite excretion and a particularly high VMA/HVA ratio (2.87), supporting earlier data of Laug *et al.* [9]. The urinary catecholamine excretion appeared to be 15% more sensitive than the determination of serum VMA and HVA; however, the serum data have proved to be very helpful tumour markers in those children with abnormal values at diagnosis [26] and good prognostic indicators in patients with and even without increased values.

More mature biochemical pattern (VMA/HVA $>$ stage related median) was not correlated with more differentiated histology as judged by the modified Hughes' grading system [19]. Surprisingly in patients with localised neuroblastoma the opposite was the case, with an association of low VMA/HVA (< 0.7) with the most mature histological grade 1. The small numbers in each group warrant a cautious interpretation of this finding, although the particular high VMA/HVA ratios and low-grade histological differentiation in stage IVS infants supports this view.

The serum VMA/HVA ratio did not provide prognostic information for patients with stage IVS and stage IV. In contrast, children with localised neuroblastoma were discriminated into a good prognosis group (EFS 81%) with a VMA/HVA ratio ≥ 0.70 and a poor prognosis group (EFS 48%) with a ratio < 0.70. The prognostic impact was independent of other known factors such as ferritin [22] and neuron-specific enolase [23, 24], but may be partially expressed by LDH [25]. The inability of earlier studies to derive prognostic information from the urinary VMA/HVA ratio for stage I–III neuroblastoma [8–11] may be mainly due to the limited number of patients. Our considerably longer observation time (mean: 6.17 years), the use of serum as source instead of urine and of different reference value definitions, may also explain these differences in part. In addition, the fact that all serum HVA and VMA levels were determined in the same laboratory using the same methods and reference values throughout the study makes a comparison between different patients over a long period of time much more reliable. Similar reasons may be responsible for the failing prognostic impact of VMA/HVA in stage IV patients as observed by other investigators [10].

In conclusion, serum VMA and HVA determinations may be valuable stage-dependent tumour markers for children with neuroblastoma and may help to estimate the EFS prognosis. A more mature biochemical pattern did not indicate a more differentiated histology.

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Treatment of Poor Prognosis Burkitt's Lymphoma in Adults with the Société Française d'Oncologie Pédiatrique LMB Protocol—A Study of the Federation Nationale des Centres de Lutte Contre le Cancer (FNLCC)

T. Philip, R. Meckenstock, E. Deconnick, C. Carrie, C. Bailly, P. Colombat, C. Dauriac, M. C. Demaille, B. Salles, J. Y. Cahn, F. Turpin and P. Biron

14 adult patients between 16 and 50 years old with small non-cleaved cell lymphoma (Burkitt's lymphoma) were prospectively treated from 1982 to 1990 with the LMB protocols of the Société Française d'Oncologie Pédiatrique (SFOP). No HIV-positive patients were included. All patients had extensive disease with bad prognosis factors, i.e. 10 patients had Murphy stage III and 4 had stage IV with bone marrow involvement. The LMB protocols were characterised by high-dose fractionated cyclophosphamide, high-dose methotrexate (HD-MTX), and cytosine arabinoside. No local or central nervous system irradiation was used. Treatment duration ranged from 5 (LMB 84) to 12 (LMB 81) months. There were no therapy-related deaths. All patients achieved complete remission (CR). 6 patients relapsed between 2 and 30 months following CR. 8 of the 14 patients (57%) are still alive and disease-free after treatment by LMB protocol alone. 2 patients were salvaged with bone marrow transplantation after relapse and a total of 10 out of 14 patients (71%) are disease-free at the time of this report. Our results showed the high curability of advanced Burkitt's lymphoma using a paediatric protocol, even in adult patients. The LMB protocol may be applied to adult patients but requires intensive care during the induction period.
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INTRODUCTION

CURE OF advanced aggressive lymphoma was first obtained with the MOPP protocol in 1973, and results were only slightly improved with the CHOP regimens in 1976 [1, 2]. Modern intensive and alternating drug protocols of the second and third generation such as M-BACOD, ProMACE-MOPP, ProMACE-CYTABOM and MACOP-B, for example [1, 3–8] are based since 1980 on the theoretical model of Goldie and Coldman [9] and the putative relationship between dose intensity and efficacy [10, 11]. These protcols produce long-term disease-free survival (DFS) rates of 55–70% with adult patients but results are mainly reported in large cell lymphoma and the superiority of these aggressive protocols are still a matter of debate.

Burkitt's lymphoma is diagnosed in up to 60% of paediatric