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Original contribution

HuC/D expression in small round cell tumors and neuroendocrine tumors: a useful tool for distinguishing neuroblastoma from childhood small round cell tumors☆

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Summary The RNA-binding protein HuC/D displays a neuron-specific expression and is involved in neuronal differentiation and the maintenance of the nervous system. Here we investigated the diagnostic value of HuC/D in neuroblastomas. We evaluated 85 neuroblastic tumors: 81 neuroblastomas; 3 ganglioneuroblastomas, intermixed; 1 ganglioneuroma, maturing; and 101 other tumors consisting of 34 Ewing sarcomas, 14 nephroblastomas, 11 rhabdomyosarcomas, 15 pulmonary small cell carcinomas, 18 pancreatic neuroendocrine tumors, and 9 pheochromocytomas. Immunohistochemistry for HuC/D, PHOX2B, and tyrosine hydroxylase was performed. The immunoreactivity for HuC/D was semiquantified using the total score (TS; range, 0-8). HuC/D positivity was defined as a TS ≥6. The TS of the neuroblastic tumors (mean TS, 7.94) was significantly higher than those of the other small round cell tumors and neuroendocrine tumors ($P < .001$) except for the pheochromocytomas (mean TS, 6.89; $P = .074$). HuC/D was positive in all 85 neuroblastic tumors, 1 (2.9%) Ewing sarcoma, 1 (6.7%) pulmonary small cell carcinoma, and 8 (89%) pheochromocytomas. PHOX2B was positive in all of the neuroblastic tumors and pheochromocytomas. Tyrosine hydroxylase was positive in 80 (94%) neuroblastic tumors, 1 (9.1%) rhabdomyosarcoma, and all of the pheochromocytomas. Therefore, HuC/D serves as a highly sensitive diagnostic marker to distinguish neuroblastomas from other small round cell tumors. The combination of HuC/D and PHOX2B staining may be valuable for the diagnosis of neuroblastic tumors, especially in the assessment of small sections. HuC/D expression in tumors may be related to catecholamine production or a neural crest–derived cell origin.

☆ Competing interests: The authors declare that there are no conflicts of interest to disclose.

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1. Introduction

Neuroblastomas are small round cell tumors that arise mostly in the adrenal glands and sympathetic nervous system. They are the most common extracranial solid tumor in children. Spontaneous regression and maturation to a benign ganglioneuroma are the characteristic features of neuroblastomas [1-5], and it is also known that chemotherapy leads to the maturation of neuroblastoma cells. Neuroblastoma cells are typically positive for neural antibodies (eg, neuron-specific enolase, synaptophysin, chromogranin A, NB84, and S-100 protein) [6,7], but these antibodies are not specific to neuroblastoma [8,9]. Tyrosine hydroxylase (TH) was the most widely used sympathoadrenal marker specific for neuroblastoma, but its sensitivity was insufficient (84%) [10,11]. The protein known as paired-like homeobox 2b (PHOX2B) has recently attracted attention as a sensitive and specific marker for neuroblastoma.

HuC/D, a member of the Hu family, is an RNA-binding protein that displays a neuron-specific expression and is involved in neuronal differentiation and the maintenance of the nervous system [12,13]. It has also been reported that HuC/D is a credible pan-neuronal marker for the enteric nervous system neurons [14,15]. However, there are few published studies about HuC/D expression in neuroblastoma.

We conducted the present study to determine the HuC/D expression along with PHOX2B and TH expressions in neuroblastomas, small round cell tumors, and neuroendocrine tumors, and we discuss the potential utility of HuC/D expression as a differential diagnostic tool in neuroblastoma.

2. Materials and methods

2.1. Patients and tissue samples

This study was approved by the Ethics Committee of Kyushu University (no. 29-429). We examined 85 paraffin-embedded samples from neuroblastic tumor tissue registered in the Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, between 1996 and 2015. Clinicopathological data were obtained from the patients' medical charts. We also stained (as comparison samples) other small round cell tumors and neuroendocrine tumors, comprising 34 Ewing sarcomas, 14 nephroblastomas, 11 rhabdomyosarcomas (5 alveolar rhabdomyosarcomas and 6 embryonal rhabdomyosarcomas), 15 pulmonary small cell carcinomas, 18 pancreatic neuroendocrine tumors, and 9 pheochromocytomas.

One Ewing sarcoma case and 1 pulmonary small cell carcinoma case were excluded from the analyses of PHOX2B and TH expression because of a shortage of tissue samples.

2.2. Histologic review

In all cases, the diagnosis was based on a light microscopic examination with hematoxylin-eosin staining according to the most recent World Health Organization classification [16]. In addition, immunoperoxidase procedures were performed using the streptavidin-biotin peroxidase method (Histofine; Nichirei Biosciences, Tokyo, Japan) or the universal immunoperoxidase polymer method (Envision-kit; Dako Japan, Tokyo, Japan) when necessary. Each sample was from a different patient.

2.3. Immunohistochemistry

The immunohistochemical study was performed using the streptavidin-biotin-peroxidase method. The primary antibodies used in this study were anti-HuC/HuD neuronal protein (mouse monoclonal, clone 16A11; A21271; dilution 1:400; Life Technologies, Carlsbad, CA), anti-PHOX2B antibody (rabbit monoclonal, clone EPR14423; no. ab183742; dilution 1:500; Abcam, Cambridge, MA), and anti-TH antibody (rabbit polyclonal; no. ab112; dilution 1:500; Abcam). Ganglion cells from small intestine were used as a positive control.

Three pathologists (J. T., M. K., and K. K.) evaluated the stained sections according to the following criteria. The intensity of HuC/D nuclear staining (intensity score [IS]) was scored from 0 to 3 as follows: 0, none; 1, weak; 2, moderate; and 3, strong. The extent of staining (proportion score [PS]) was graded as follows: 0, absent; 1, <1%; 2, 1%–9%; 3, 10% to 32%; 4, 33% to 66%; and 5, >66% of tumor cells. The total score (TS) was calculated by adding the IS and PS (IS + PS), so that the possible scores ranged from 0 to 8 [17]. HuC/D positivity was defined as a TS ≥6.

The extent of PHOX2B and TH immunoreactivity was graded according to the percentage of positive tumor cells as follows: 0, absent; 1+, <5%; 2+, 5% to 50%; 3+, 51% to 75%; and 4+, 76% to 100% of tumor cells. Positivity for PHOX2B and TH was defined as grade ≥2+ [18].

2.4. Statistical analysis

Categorical variables were compared using the Pearson χ^2 est or Fisher exact test as appropriate. Statistical significance was defined as $P < .05$. All analyses were performed with the JMP Pro statistical software package (ver. 13.1.0; SAS Institute, Cary, NC).

3. Results

3.1. Clinicopathological characteristics

The clinicopathological features of the patients with neuroblastic tumors and the comparative tumors are summarized in Tables 1 and 2. In the group of neuroblastic tumor cases, all 85 patients were children (median age, 0 years; range, 0-8 years).

3.2. HuC/D expression

The results of the immunohistochemical analysis are summarized in Table 3. In regard to extent of staining, 98% (83/

Table 1 Clinicopathological characteristics of neuroblastic tumors

Characteristics	n
Sex	
Male	52
Female	33
Age (y)	
<1.5	52
1.5≤, <5	30
5≤	3
Site	
Adrenal gland	45
Retroperitoneum	25
Others	15
Subtype	
Neuroblastoma, undifferentiated	2
Neuroblastoma, poorly differentiated	78
Neuroblastoma, differentiating	1
Ganglioneuroblastoma	3
Ganglioneuroma, maturing	1
Stage	
1	24
2A	12
2B	1
3	11
4	29
4s	3
Unknown	5
N-myc	
Positive	17
Negative	68

85) of the neuroblastic tumors showed a PS value of 5 (Figure A). In these cases, the percentage of positive tumor cells was almost 100%. Two (2%) tumors, which were the undifferentiated subtype, showed a PS of 4 (Figure B). In the ganglioneuroblastomas and ganglioneuroma, immature and mature ganglion cells were positive for nuclear and cytoplasmic staining, but Schwann cells were negative (Figure C).

In contrast, none of the Ewing sarcomas (Supplementary Fig. 1A), nephroblastomas (Supplementary Fig. 1B), rhabdomyosarcomas (Supplementary Fig. 1C), pulmonary small cell carcinomas (Supplementary Fig. 1D), and pancreatic neuroendocrine tumors (Supplementary Fig. 1E) showed a PS of 5 for HuC/D immunoreactivity. The remaining pheochromocytomas had a PS 5 in 8 of the 9 cases (89%; Supplementary Fig. 1F).

From the viewpoint of intensity, 96% (82/85) of the neuroblastic tumors, 9% (3/34) of the Ewing sarcomas, and 33% (3/9) of the pheochromocytomas had the IS value of 3. All of the nephroblastomas, rhabdomyosarcomas, pulmonary small cell carcinomas, and pancreatic neuroendocrine tumors had an IS <3.

The TS values were significantly higher in the neuroblastomas compared with the other small round cell tumors and neuroendocrine tumors ($P < .001$), except for the pheochromocytomas ($P = .074$). Regarding the immunohistochemical positivity of HuC/D, all 85 (100%) neuroblastomas, 1 (2.9%) of the 34 Ewing sarcomas, none of 14 nephroblastomas, and none of the 11 rhabdomyosarcomas were interpreted as positive. The single HuC/D-positive Ewing sarcoma showed PS 3 and IS 3. Among the neuroendocrine tumors, 8 (89%) of the 9 pheochromocytomas, 1 (6.7%) of the 15 pulmonary small cell carcinomas, and none of the 18 pancreatic neuroendocrine tumors were positive for HuC/D.

3.3. PHOX2B and TH expression

The immunohistochemical results for PHOX2B and TH expression are summarized in Table 4. All 85 of the neuroblastic tumors (Figure D-F) and all 9 of the pheochromocytomas were positive for PHOX2B. In contrast, PHOX2B expression was completely absent in the Ewing sarcomas, nephroblastomas, rhabdomyosarcomas, pulmonary small cell carcinomas, and pancreatic neuroendocrine tumors.

Eighty (94%) of the 85 neuroblastic tumors (Figure G-I), 1 of the 11 rhabdomyosarcomas, 3 of the 18 pancreatic NETs, and all 9 of the pheochromocytomas were positive for TH. In the Ewing sarcomas, nephroblastomas, pulmonary small cell carcinomas, and pancreatic neuroendocrine tumors, the TH expression was 0 or 1+.

4. Discussion

In this study, we evaluated the immunohistochemical HuC/D expression profile in neuroblastic tumors, small round cell

Table 2 Clinicopathological characteristics of small round cell tumors and neuroendocrine tumors

Tumor type	ES	WT	RMS	SCLC	Pancreatic NET	PCC
n	34	14	11	15	18	9
Sex, n (%)						
Male	13 (38)	8 (57)	3 (27)	12 (80)	5 (28)	2 (22)
Female	21 (62)	6 (43)	8 (73)	3 (20)	13 (72)	7 (78)
Age (y), mean (range)	17 (1-74)	1 (0-10)	2 (0-17)	74 (60-84)	59 (20-79)	56 (21-76)

Abbreviations: ES, Ewing sarcoma; NET, neuroendocrine tumor; PCC, pheochromocytoma; RMS, rhabdomyosarcoma; SCLC, small cell lung cancer (pulmonary small cell carcinoma); WT, Wilms tumor (nephroblastoma).

Table 3 Summary of HuC/D immunohistochemical total scoring

Tumor type	NB	Other small round cell tumors			Other neuroendocrine tumors		
		ES	WT	RMS	SCLC	Pan-NET	PCC
n	85	34	14	11	15	18	9
HuC/D positive [a]	85	1	0	0	1	0	8
(%)	(100)	(2.9)	(0)	(0)	(6.7)	(0)	(89)
8	82	0	0	0	0	0	3
7	1	0	0	0	0	0	5
6	2	1	0	0	1	0	0
0-5	0	33	14	11	14	18	1
Mean TS	7.94	1.5	0.43	0.82	3.73	1.28	6.89

Abbreviations: ES, Ewing sarcoma; NB, neuroblastoma; Pan-NET, pancreatic neuroendocrine tumor; PCC, pheochromocytoma; RMS, rhabdomyosarcoma; SCLC, small cell lung cancer (pulmonary small cell carcinoma); WT, Wilms tumor (nephroblastoma).

[a] HuC/D positivity was defined as the TS ≥6.

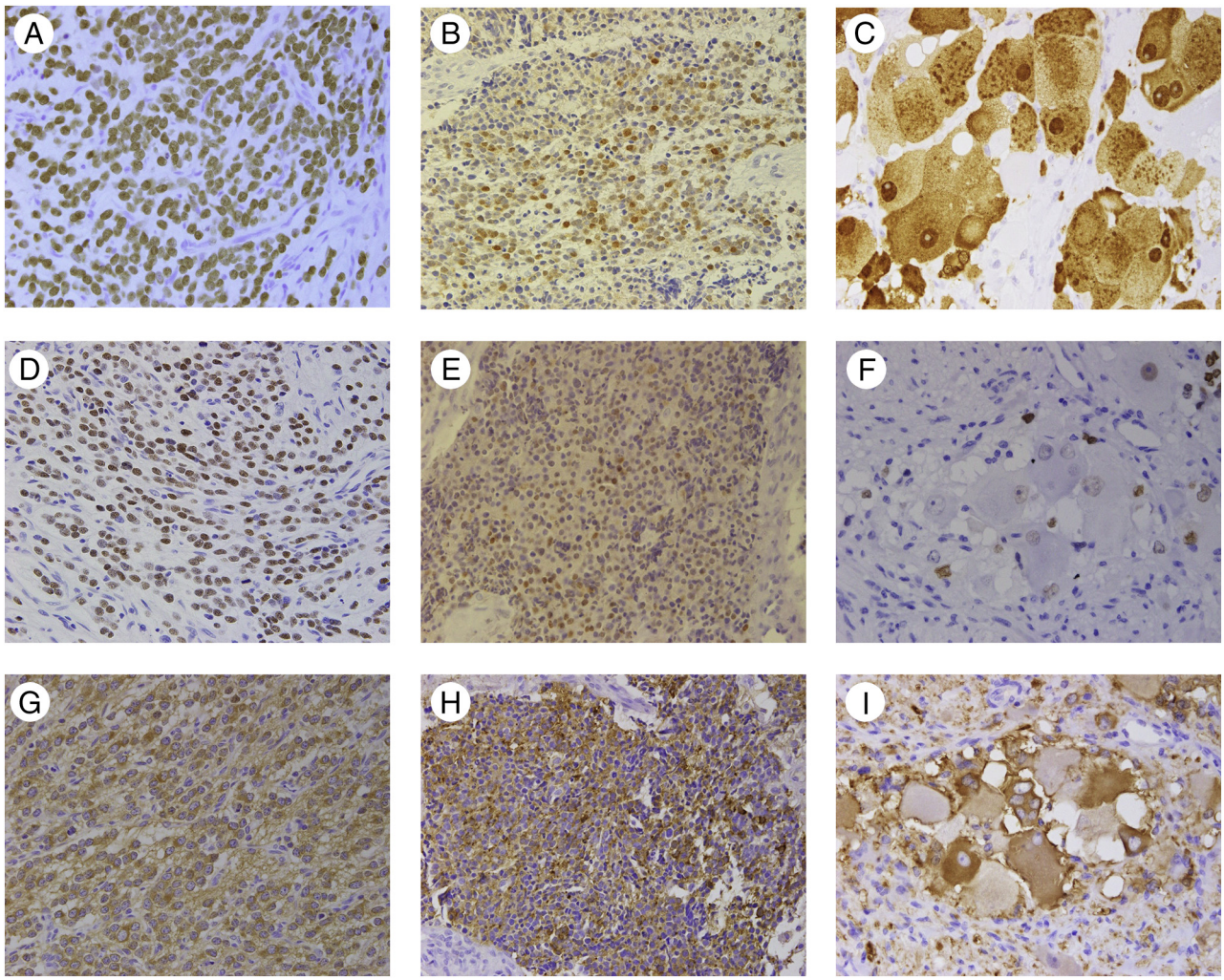

Figure Examples of HuC/D (A-C), PHOX2B (D-F), and TH (G-I) staining in the neuroblastic tumors. A, D, and G, Adrenal neuroblastoma, poorly differentiated in a 1-year-old boy. A, HuC/D (TS 8 [PS 5 + IS 3]). D, PHOX2B (4+). G, TH (4+). B, E, and H, Intra-abdominal undifferentiated neuroblastoma in a 2-year-old girl. B, HuC/D (TS 6 [PS 4 + IS 2]). E, PHOX2B (2+). H, TH (4+). C, F, and I, Adrenal ganglioneuroblastoma, intermixed in a 4-year-old boy. C, HuC/D (TS 8 [PS 5 + IS 3]). F, PHOX2B (3+). I, TH (4+).

Table 4 Summary of PHOX2B and TH immunohistochemical scoring

Tumor type	NB	Other small round cell tumors			Other neuroendocrine tumors		
		ES	WT	RMS	SCLC	Pan-NET	PCC
n	85	33	14	11	14	18	9
PHOX2B							
PHOX2B positive [a]	85	0	0	0	0	0	9
(%)	(100)	(0)	(0)	(0)	(0)	(0)	(100)
4+	67	0	0	0	0	0	8
3+	10	0	0	0	0	0	1
2+	8	0	0	0	0	0	0
0-1+	0	33	14	11	14	18	0
TH							
TH positive [a]	80	0	0	1	0	3	9
(%)	(94)	(0)	(0)	(9)	(0)	(17)	(100)
4+	70	0	0	0	0	0	9
3+	2	0	0	0	0	0	0
2+	8	0	0	1	0	3	0
0-1+	5	33	14	10	14	15	0

Abbreviations: ES, Ewing sarcoma; NB, neuroblastoma; Pan-NET, pancreatic neuroendocrine tumor; PCC, pheochromocytoma; RMS, rhabdomyosarcoma; SCLC, small cell lung cancer (pulmonary small cell carcinoma); WT, Wilms tumor (nephroblastoma).

[a] PHOX2B and TH positivity was defined as the score ≥2+.

tumors, and neuroendocrine tumors. The results showed that HuC/D was expressed more diffusely and strongly in the neuroblastic tumors than in the other tumors, with the exception of the pheochromocytomas.

It is of note that HuC/D was reported to be a useful panneuronal marker in both central and enteric nervous system neurons [12-15]. Few studies have addressed the expression of Hu antigens in small round cell tumors. Dalmau et al et al [19], using frozen tumor tissue and anti-Hu IgG (prepared from the sera of patients with paraneoplastic sensory neuropathy/encephalomyelitis) for immunohistochemical and Western blot analyses, observed evidence of Hu expression in 4 of 8 neuroblastomas and both of 2 Ewing sarcomas. One rhabdomyosarcoma was negative for Hu antigen [19]. In another study of neuroblastomas, Gultekin et al [20] found that 39 (78%) of 50 neuroblastomas expressed the Hu antigens. However, HuC/D immunohistochemistry in small round cell tumors and neuroendocrine tumors has not been systematically conducted to investigate HuC/D as a diagnostic marker for neuroblastomas.

PHOX2B has been described as a sensitive and highly specific immunohistochemical marker for peripheral neuroblastic tumors [21], including neuroblastoma, with 92% sensitivity and 100% specificity [18]. In our present study, HuC/D expression was detected with diffuse (PS 4-5) staining in all 85 neuroblastic tumor cases and with strong (IS 3) staining in 82 (96%) cases; in addition, we observed positive HuC/D expression in neuroblastic tumors with 100% sensitivity and 98% specificity among small round cell tumors (neuroblastic tumors, nephroblastomas, Ewing sarcomas, and rhabdomyosarcomas). The positive expression of PHOX2B and TH showed 100% and 94% sensitivity and 100% and 98% specificity, respectively. In 8 (9%) cases, grade 2+ PHOX2B expression was detected. Therefore, the evaluation of HuC/D immunoexpression may be a highly sensitive diagnostic tool to distinguish neuroblastomas from other pediatric small round cell tumors.

The histologic definitive diagnosis of neuroblastoma is sometimes challenging because of small specimens with suboptimal histology, such as specimens of bone marrow, which is the most common site of infiltration in children presenting with metastatic disease at the time of diagnosis and also a frequent site of recurrences [22]. Burchill et al [23] stated that for bone marrow disease assessments in children with neuroblastomas, the value of immunohistochemistry depends on the quality of the sample and the specificity and sensitivity of the antibodies, and they encouraged the use of at least 2 antibodies. Thus, the combination of HuC/D and PHOX2B staining may be especially valuable in the assessment of small sections.

Our study included 2 neuroblastomas of the undifferentiated subtype. These 2 cases were both TS 6 (PS 4 and IS 2), which is lower than the TS values of the neuroblastomas of the poorly differentiated subtype, 99% (77/78) of which were TS 8 (PHOX2B expression in these cases was 3+ and 2+, and TH expression was 4+ and 1+, respectively). It was reported that HuC/D may be used as a specific marker in progenitor cell cultures for the identification of "postmitotic" ganglion cells [12]. Wakamatsu and Weston [24] reported that Hu genes displayed sequential expression during neuronal differentiation, and that HuC and HuD were not detected in apparently undifferentiated cell populations. These reports suggest the association between the differentiation of neuroblastoma cells and HuC/D expression, although the number of undifferentiated subtype cases in the present study was very limited. Further studies using a larger number of cases are required to confirm

the utility of HuC/D and to compare this with PHOX2B and TH in undifferentiated subtype cases.

Among the neuroendocrine tumors that we examined, the pheochromocytomas showed a level of protein expression that was comparable to that of the neuroblastic tumors, and significantly higher TS values than the pulmonary small cell carcinomas ($P < .001$) and pancreatic neuroendocrine tumors ($P < .001$). Neuroblastic tumors and pheochromocytomas are both catecholamine-producing tumors, and they are derived from the adrenal glands and sympathetic nervous system, which are neural crest–derived tissues [25]. These similarities indicate that catecholamine-production or neural crest–derived cell origin may be related to the expression of HuC/D. Histologically, a pheochromocytoma is not a small round blue-cell tumor. Therefore, it is not difficult to distinguish neuroblastomas from pheochromocytomas without using Hu/D immunochemistry in clinical practice.

In conclusion, our findings indicate that HuC/D may serve as a highly sensitive diagnostic marker for diagnosing neuroblastoma. The combination of HuC/D and PHOX2B staining may be valuable in this regard, especially in assessments of small sections. The expression of HuC/D in tumors may be related to a catecholamine production or neural crest–derived cell origin.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2018.11.004.

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