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Maturation of Neuroblastomas

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STARVATION (i.e. serum-free medium) can induce differentiation of various cell lines *in vitro* [1]. Retinoic acid and other drugs may also induce differentiation of some neuroblastoma cell lines [2, 3], and decreased N-*myc* expression precedes morphological differentiation *in vitro* [2]. Spontaneous maturation of neuroblastomas has been extraordinarily observed [4, 5]; however, it may represent the same phenomenon as spontaneous regression, i.e. undifferentiated neuroblastoma-cell kill with subsequent overgrowth of the mature ganglioneuroma tumour elements [5]. Spontaneous regression and maturation of neuroblastomas were documented in less than 2% of cases in Denmark [5].

Studies have suggested a maturational effect of specific treatment regimens of neuroblastoma [6], but the results are questionable because the possibility of cytoreduction of the most undifferentiated cells was ignored [4, 7]. A cytoreductive effect of intratumoral injection of Coley's toxin, a potent liberator of tumour necrosis factor, probably explains the case of spontaneous maturation of a neuroblastoma reported by Cushing and Wolbach [8]. Intralesional injection of interferon may induce tumour shrinkage also [9], but systemic treatment has been disappointing [9, 10].

We have studied tumour specimens in 35 of 46 consecutive neuroblastoma patients in our department from 1970 to 1980. In 7 cases, samples were retrieved from the primary tumour in the same patient both before and after adjuvant treatment. In all 4 responders, the tumour showed morphological maturation after treatment. However, in only 1 of 3 relapsing tumours was the histological picture slightly more "mature" than before treatment.

We believe that this maturational effect of treatment simply represents cytoreduction of the most undifferentiated cells in responding tumours. Therefore, studies claiming a maturational effect of specific treatments should be reviewed with caution.

1. Sugimoto T, Sawada T, Negoro S, *et al.* Altered expression of cell surface membrane antigens in a common acute lymphoblastic leukemia-associated antigen-expressing neuroblastoma cell line (SJ-N-CG) with morphological differentiation. *Cancer Res* 1985, **45**, 358–364.
2. Thiele CJ, Reynolds CP, Israel MA. Decreased expression of N-*myc* precedes retinoic acid-induced morphological differentiation of human neuroblastoma. *Nature* 1985, **313**, 404–406.
3. Preis PN, Hochhaus G, Saya H, Levin V, Sadee W. Differentiation of human neuroblastoma cells by retinoic acid plus herbimycin-A (abstr.). *Proc ASCO* 1988, **7**, 264.
4. Pritchard J, Kemshead J. Neuroblastoma: recent developments in assessment and management. In: Duncan EW, ed. *Paediatric Oncology*. Heidelberg, Springer, 1983, 69–78.
5. Carlsen NLT. How frequent is spontaneous remission of neuroblastoma? Implications for screening. *Br J Cancer* 1990, **61**, 441–446.
6. Raaf JH, Cangir A, Luna M. Induction of neuroblastoma maturation by a new chemotherapy protocol. *Med Pediatr Oncol* 1982, **10**, 275–282.
7. Nitschke R, Cangir A, Crist W, Berry DH. Intensive chemotherapy for metastatic neuroblastoma: a Southwest Oncology Group study. *Med Pediatr Oncol* 1980, **8**, 281–288.
8. Cushing H, Wolbach SB. The transformation of a malignant paravertebral sympathicoblastoma into a benign ganglioneuroma. *Am J Pathol* 1927, **3**, 203–216.
9. Sawada T, Fujita T, Kusunoki T, Imanishi J, Kishida T. Preliminary report on the clinical use of human leukocyte interferon in neuroblastoma. *Cancer Treat Rep* 1979, **63**, 2111–2113.
10. Berthold F, Kaatsch P, Evers G, *et al.* Intensive kombinationschemotherapie und β-Interferon zur behandlung von kindern mit metastasiertem neuroblastoma: Studie GPO-NB 79/82. *Kin Pädiat* 1984, **196**, 143–149.

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Acute Reversible Neurotoxicity after Intrathecal Low-dose Methotrexate

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CEREBROSPINAL FLUID (CSF) is a sanctuary for malignant cells during systemic chemotherapy, and may cause rapid expansion of malignancy in the central nervous system (CNS). Intrathecal administration of methotrexate results in effective drug concentrations in CSF. However, methotrexate is potentially neurotoxic, and adverse CNS effects have been described following intrathecal administration: meningoencephalitis, beginning 2–4 h after therapy and lasting 12–72 h; transient or permanent paraplegia starting 0.5–48 h (occasionally 1–2 weeks) after treatment and improving between 48 h and 2–5 months afterwards; and permanent, progressive leukoencephalopathy, occurring months to years after onset of treatment [1]. An acute transient neurological dysfunction has also been reported, occurring 1 week after the second course of high-dose intravenous methotrexate [2]. We report our case of acute transient CNS toxicity after intrathecal methotrexate administration.

A 60-year-old woman with breast carcinoma was admitted with sudden spastic ataxia of the legs. CSF analysis found meningeal carcinomatosis, and a scan of the cerebrum ruled out parenchymal metastases. An intraventricular Ommaya reservoir was applied, and methotrexate 5 mg was administered. After 1 day, neurological symptoms had disappeared and the CSF was cleared of malignant cells. After 6 days, the CSF methotrexate concentration fell below the critical level of 0.2×10^{-6} mol/l (Table 1) and a second dose of methotrexate 5 mg was given. Five days later, the patient had expressive aphasia, and neurological examination found Babinski's reflexes on both sides. CSF

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