Neuroblastoma: an enigmatic disease

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Neuroblastoma is the most common extra-cranial solid tumor of childhood[1]. It originates in cells of the neural crest, and so can be found anywhere along the paravertebral sympathetic chain or in the adrenal gland. In the last 15 years, new developments in the genetics and biology of neuroblastoma, have led to a better understanding of the natural history and prognostic features of this cancer. The presence of identifying biochemical markers detectable in the urine of patients with neuroblastoma, as well as the remarkably inferior survival of children diagnosed at more than 12 months of age, have led some groups to screen infants for neuroblastoma, in the hope of decreasing both overall mortality, as well as the incidence of advanced stage disease. This article reviews some clinical aspects of neuroblastoma, but emphasizes the genetic and biologic features in relation to prognosis and treatment. Finally, we discuss the different screening experiences for this disease, in particular from the Quebec Neuroblastoma Screening Project.

Neuroblastoma affects approximately 1/7,000 children under the age of 5 years[2], and is very rarely diagnosed beyond the age of 10 years (36% of patients being less than 1 year of age, 79% less than 4 years and only 3% being diagnosed after the age of 10)[1]. This neural crest-derived tumor has many unique aspects, and shows great heterogeneity. Neuroblastoma occasionally spontaneously regresses, or differentiates into a benign lesion. Microscopic neuroblastic nodules, histologically identical to neuroblastoma, are found in the adrenal gland of a high percentage of fetuses and young infants dying of other causes[3,4]. These findings suggest that these nodules represent a normal embryonic stage in the development of the adrenal gland. Their failure to regress or mature may result in the development of malignant neuroblastoma. In contrast to the spontaneous regression which may occur, neuroblastoma may also behave as a very aggressive malignant tumor.

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Biology

The biologic characteristics and clinical heterogeneity of neuroblastoma make it unique among pediatric tumors. Based on our current knowledge, it is likely that neuroblastoma represents at least two distinct clinical/biologic entities[5]. Recent research at the cellular and molecular level has helped to clarify this distinction[6].

One of the most characteristic and consistent cytogenetic anomalies identified in neuroblastoma is the deletion of the short arm of chromosome 1 (loss of heterozygosity, LOH) resulting in partial 1p monosomy[6], thought to represent the loss of a suppressor gene in part responsible for development of neuroblastoma[1,6]. This allelic loss of chromosome 1p has been found to be strongly prognostic both in localized and disseminated neuroblastoma, in both younger ($\leqslant 12$ months of age) and older (> 12 months of age) children[7]. Some groups have also demonstrated the occurrence of loss of heterozygosity on chromosome 14q in some cases of neuroblastoma, suggesting a possibility of genetic heterogeneity in this tumor[6].

About 25–30% of children with neuroblastoma have *N-myc* gene amplification in their tumors[6]. Initial cytogenetic analyses of human neuroblastomas had identified the presence of extrachromosomal double-minute chromatin bodies (dmin) and/or homogeneously staining regions on different chromosomes. Those two abnormalities were later found to represent *N-myc* gene amplification[8]. Amplification of *N-myc* is found in more than 30% of patients with advanced stages but in only 5–10% of patients with earlier stages[6]. It is associated with rapidly progressive disease and poor prognosis, regardless of the clinical stage[9–11]. Moreover, studies by Brodeur *et al.* demonstrated that the *N-myc* copy number in a given tumor is usually consistent at different tumor sites and also over time[12]. These findings suggest that the presence or absence of *N-myc* amplification is an intrinsic biologic property of the tumor. Finally, there is a correlation between the presence of *N-myc* amplification and the loss of heterozygosity of chromosome 1p, with the two findings being strongly predictive of poor prognosis[6,7]. Allelic loss of chromosome 1p may select a larger population of poor-risk patients, with the *N-myc* amplified tumors being a particularly unfavorable subset[7].

The DNA content of neuroblastoma tumor has also proven to be of great help in predicting the outcome of patients and their response to therapy, especially in infants less than 1 year of age with advanced stage disease. Look *et al.*[13] were the first to report the analysis of DNA content in the tumor tissue of 35 infants with neuroblastoma. They found a correlation between abnormally high DNA content and low stage tumors with a good response to chemotherapy. Further studies confirmed the prognostic significance of flow-cytometric analysis of DNA-index

(DI)[10,14]. Hyperdiploidy [especially near triploidy, DI(1,25–1,75)] predicts a favorable outcome and good response to chemotherapy even in unresectable disease, as opposed to near-diploidy (or near tetraploidy) which is more likely to be associated with an adverse outcome. Again, analysis of multiple samples of tumor for DNA content showed great consistency within different areas of the same tumor and in tumor sampled at different times during the course of therapy[15]. Finally, there is generally a good correlation between *N-myc* amplification and near-diploidy in a given tumor[10,15].

Based on these cytogenetic, molecular and flow cytometric analysis, and also based on the long known clinical prognostic features (age and stage at diagnosis), Brodeur *et al.*[6] suggested a clinical/genetic classification of neuroblastoma patients into three distinct risk-groups (Table 1) to allow for the planning of more specific risk-adapted therapy.

The ability of neuroblastoma to differentiate either spontaneously or in response to treatment has led many authors to study the expression of the nerve growth factor (NGF) receptor, and the response to NGF of neuroblastoma cells. The principal component of the NGF receptor is encoded by the TRK-proto-oncogene. Nakagawara *et al.*[16] studied the expression of *TRK* mRNA in frozen tumor samples from 77 patients with neuroblastoma. They found a strong correlation between *TRK* expression and favorable tumor stage, young age, and normal *N-myc* copy number. In addition, *N-myc* amplification was associated with low expression of *TRK* and poor prognosis. *TRK* expression had an independent prognostic value only in tumors with unamplified *N-myc*. It is still uncertain what precise role NGF and its receptor play in the development and progression or regression of neuroblastoma, although high *TRK* expression may favorably influence a subset of tumors, via the NGF-receptor pathway. Similar findings have been reported by Kogner *et al.*[17].

Aberrations of chromosome 17 have been shown to occur with increased frequency in neuroblastoma. The frequent occurrence of p53

Table 1 Clinical/genetic types of neuroblastoma

Feature	Type 1	Type 2	Type 3
Age	< 12 months	Any age	Any age
Stage	I, II, IV-S	III, IV	Any stage
Ploidy	Hyperdiploid	Near diploid	Near diploid
	Near triploid	Near tetraploid	Near tetraploid
Chromosome 1p	Normal	Normal	Deleted
dmins, HSR	Absent	Absent	Present
N-myc copy	Normal	Normal	Amplified
Outcome	Good	Intermediate	Bad

dmins, double-minute chromatin bodies; HSR, homogeneously staining region
From Brodeur *et al* (1992)[6]

mutations in many human neoplasms, together with the location of the p53 tumor suppressor gene on chromosome 17, led Vogan *et al.*[18] from the Quebec Neuroblastoma Screening Study[19] to examine 38 primary tumors for the presence of p53 mutations. They found no p53 abnormality and concluded that the chromosome 17 alterations in neuroblastoma involve other genes.

The multidrug resistance (MDR) gene product P-glycoprotein has been found by some groups to be of prognostic importance in neuroblastoma[20]. More recently, another protein leading to decreased intracellular concentrations of natural product antineoplastic drugs, the multidrug resistance protein (MRP), has been shown to have prognostic significance in neuroblastoma[21]. MRP may also mediate resistance to agents important in the therapy of neuroblastoma such as cyclophosphamide and cisplatinum by extrusion of their glutathione conjugated metabolites[21].

Other biologic variables to consider with respect to prognosis of neuroblastoma include several serum markers: ferritin, neuron-specific enolase (NSE), ganglioside GD_2, and lactic dehydrogenase (LDH). All have been and continue to be included in many large neuroblastoma studies. Each has some predictive prognostic value. Their specificity and sensitivity are variable, and their precise independent power in predicting prognosis compared to the clinical and genetic variables already described may be limited[1,7].

Clinical aspects[1]

Clinical presentation

The majority of primary tumors (65%) occur in the abdomen, either in the adrenal, or in the paravertebral sympathetic ganglia. Thoracic primaries are found in approximately 20% of cases. A minority of patients have their primary tumor in the neck (1–5%) or pelvis (2–3%). Rarely, a primary tumor cannot be found or there may be multiple primaries

Extension of disease can occur via either the lymphatic (regional or distant lymph nodes) or the hematogenous route. Typical sites of metastasis are bone marrow, bone, liver and skin. Low stage disease (INSS[22] 1,2,4-S) is seen in a larger proportion of infants ($\leqslant$ 1 year) than older children, whereas disseminated disease occurs in at least 50% of patients older than 1 year of age. Whatever the stage, infants have a better outcome than older children.

The signs and symptoms at presentation depend on both the location of the primary mass and the metastases (if any). Abdominal or pelvic primaries can cause discomfort, gastrointestinal tract dysfunction or compression, urologic obstruction, venous and lymphatic compression syndromes, and occasionally, renin-mediated hypertension. Young infants with stage 4-S disease may present with massive liver enlargement leading to respiratory insufficiency and other complications. Neck and thoracic masses may cause mechanical compression resulting in respiratory distress, Horner's syndrome, or superior vena cava syndrome. Disseminated disease can present with proptosis and periorbital ecchymoses (retrobulbar and orbital infiltration), bone pain and irritability (bone and marrow disease), skin nodules, as well as constitutional symptoms. Finally, two classic but rare paraneoplastic syndromes occur in some patients: opsomyoclonus and/or cerebellar ataxia, and severe diarrhea secondary to secretion of vasoactive intestinal peptide (VIP). On the other hand, asymptomatic neuroblastomas may occasionally be found by imaging alone for other reasons, either postnatally or antenatally.

Diagnosis and staging

Before 1988, there were no published established uniform criteria for the diagnosis of neuroblastoma, its staging and response to treatment. An international group of experts met in 1986 to reach a consensus on these different issues and established the International Criteria for Neuroblastoma Diagnosis, Staging and Response to Treatment[22], which were then revised and published in 1993[23]. Minimal criteria for the diagnosis of neuroblastoma are:

1. An unequivocal pathologic diagnosis made from tumor tissue by standard methods, including immunohistology or electron microscopy if necessary; or
2. Bone marrow containing unequivocal tumor cells (e.g. syncytia or immunohistologically positive cells) **and** urine containing increased urinary catecholamine metabolites (VMA and/or HVA $\geqslant$ 3 SD above the mean per mg creatinine, corrected for age). Minimum tests are recommended to determine the extent of disease in the abdomen, chest, bone and bone marrow (see[23] for details).

With the growing evidence that many biologic and genetic features of tumor tissue are very informative with respect to prognosis, it is strongly recommended that such analysis be performed at diagnosis. DNA index,

N-myc copy number, chromosome 1 deletion and *TRK*-A expression should be sought whenever possible. Tumor histology and, to some extent, certain serum factors (ferritin, NSE, LDH and others) also possess some prognostic significance and should be analysed in most patients.

Many different systems have been used for staging neuroblastoma. The International Neuroblastoma Staging System (INSS)[22] uses the most important elements of each previous system. Table 2 compares different surgicopathologic staging systems with the INSS.

Management, general principles and controversies

The management of neuroblastoma relies on three treatment modalities: surgery, chemotherapy, and radiotherapy. The indications for radiotherapy have considerably decreased with time as chemotherapy/surgery regimens have improved. Until recently, risk-grouping was based on stage and age. The low-risk group of patients included all patients with

Table 2 Comparison of staging systems for neuroblastoma

CCSG system	POG system	International (INSS)
Stage I. Tumor confined to the organ or structure of origin	Stage A. Complete gross resection of the primary tumor, with or without microscopic residual disease. Intracavitary lymph nodes not adhered to the primary tumor must be histologically free of tumor. Nodes adhered to the surface of or within the primary may be positive	Stage 1. Localized tumor confined to the area of origin; complete gross excision, with or without microscopic residual disease; identifiable ipsilateral and contralateral lymph nodes negative microscopically
Stage II. Tumor extending in continuity beyond the organ or structure of origin, but not crossing the midline. Regional lymph nodes on the ipsilateral side may be involved	Stage B. Grossly unresected primary tumor. Nodes and nodules the same as in stage A	Stage 2A. Unilateral tumor with incomplete gross excision; identifiable ispilateral and contralateral lymph nodes negative microscopically. Stage 2B. Unilateral tumor with complete of incomplete gross excision; with positive ipsilateral regional lymph nodes; identifiable contralateral lymph nodes negative microscopically
Stage III. Tumor extending in continuity beyond the midline. Regional lymph nodes may be involved bilaterally	Stage C. Complete or incomplete resection of primary. Intracavitary nodes not adhered to primary must be histologically positive for tumor. Liver as in stage A	Stage 3. Tumor infiltrating across the midline with or without regional lymph node involvement; or, unilateral tumor with contralateral regional lymph node involvement; or, midline tumor with bilateral lymph node involvement
Stage IV. Remote disease involving the skeleton, bone marrow, soft tissue and distant lymph node groups (see stage IV-S)	Stage D. Dissemination of disease beyond intracavitary nodes (i.e., extracavitary nodes, liver, skin, bone marrow, bone, etc.)	Stage 4. Dissemination of tumor to distant lymph nodes, bone, bone marrow, liver and/or other organs (except as defined in stage 4-S)
Stage IV-S. As defined in stage I or II, except for the presence of remote disease confined to the liver, skin, or marrow (without bone metastases)	Stage D-S. Infants < 1 year of age with stage IV-S disease (see CCSG)	Stage 4-S. Localized primary tumor as defined for stage 1 or 2 with dissemination limited to liver, skin and/or bone marrow

From Brodeur and Castleberry (1993)[1]

INSS stages 1 and 2A and infants ($\leqslant$ 1 year) with stages 2B, 3 and 4-S. Patients with stage 1 have an excellent 90% disease-free survival with no further treatment after surgical resection. Children with stage 2A disease and infants with stages 2B/3 may benefit from low dose and short course chemotherapy after surgery, and have been reported to achieve approximately an 85% disease-free survival. Also still debated is the overall treatment, if any, of infants with 4-S disease who have an extremely varied and unpredictable course. Regardless of the management, survival rates for this subset of patients vary from 57–90% in different reports[1].

The intermediate clinical risk-group included children ($>$ 1 year) with stages 2B/3 and infants with stage 4 disease. These patients have been treated by different groups with moderately aggressive chemotherapy (e.g. cyclophosphamide/doxorubicin $\pm$ cisplatin/teniposide). Adjuvant radiotherapy has improved the outcome for children with 2B and 3 stages. Different reported survival rates for this subgroup of patients range between 59–75%[1]. More recently, the need for additional therapy, beyond surgery in this favorable group of patients (in the absence of unfavorable biologic features) has been questioned[23a].

The prognosis of disseminated neuroblastoma in children over 1 year remains dismal despite the intensification of treatment regimens and the use of colony-stimulating factors. Even the use of bone marrow transplantation for this highest risk-group has been disappointing. These different strategies seem able to prolong remission duration, but the long term cure rate remains very low (10–30%)[24]. Recently, McCowage *et al.*[25] reported impressive results using autologous bone marrow transplantation (ABMT) for 17 patients with stage 4 disease in remission after intensive conventional chemotherapy, surgery, and tumor-bed irradiation (5 year disease-free survival of 87%). These results compare very favorably with results from previous studies. However, the selection of the patients on the basis of response to induction therapy may have introduced a positive bias, and the number of patients is too small to permit any firm conclusion. Also, as the authors state in their conclusion: 'an unresolved question concerning the use of ABMT for neuroblastoma is whether such therapy increases the ultimate cure rate'.

With the hope of improving the survival rate and cure of the subset of patients with poor prognosis neuroblastoma, while at the same time minimizing toxicity for good prognosis patients, better definition of different risk-groups is necessary. Thus, most current studies consider various biologic features in addition to stage and age (DNA index in infants and *N-myc* copy number in all patients, histology, and serum markers, among others). Brodeur and Castleberry[1] propose a prognostic classification for neuroblastoma therapy, based on both the clinical characteristics of the patients, as well as the most accepted biologic tumor features (Table 3).

Table 3 Proposed prognostic strata for neuroblastoma therapy based on clinical and biologic tumor features

Risk category	Patient age (years)	INSS stage	*N-myc* copy	DNA index
Low	⩽ 1	1,2A,2B,3,4,4-S	1	> 1
	> 1	1,2A	1	NA
Intermediate	⩽ 1	2A,2B,3,4,4-S	1	1
	> 1	2B,3	> 1	NA
High	⩽ 1	2A,2B,3,4,4-S	> 1	NA
	> 1	4	1	NA
	> 1	2A,2B,3,4	> 1	NA
Unclear	⩽ 1	1	> 1	and/or 1
	> 1	1	> 1	NA

NA = not applicable. From Brodeur and Castleberry (1993)[1]

Other newer therapeutic avenues under investigation for neuroblastoma include immunotherapy with monoclonal antibodies against the GD2 ganglioside[26] or with interleukin-2[27]. Also under investigation are the interesting differentiating effect of retinoic acid and the cytotoxic and maturational effects of deferoxamine on neuroblastoma, as well as novel (but still myelosuppressive) cytotoxic compounds such as topotecan, and the combination of topotecan with cyclophosphamide.

Screening

The initial arguments for the interest in neuroblastoma screening in different parts of the world were numerous. Briefly, approximately 90% of patients with neuroblastoma excrete one or both catecholamine metabolites, homovanillic acid (HVA), a product of dopamine metabolism, or vanillylmandelic acid (VMA), a product of norepinephrine and epinephrine metabolism. The hope was that the detection of pre-clinical neuroblastoma in infancy by urinary screening would improve the outcome by decreasing the incidence of more advanced disease in older children, so that screening would decrease the overall mortality rate.

The Japanese were the first group to institute experimental screening programs in 1973[28]. The initial screening experience in Kyoto was rapidly expanded to eight other Japanese regions, forming the Japanese Mass Screening Study Group (MSSG)[29]. In 1981, mass screening was started in Sapporo city with an improvement in the urinary screening technique (from qualitative to quantitative analysis of filter paper urine by high-performance liquid chromatography-HPLC). Encouraging results from the MSSG along with the apparent dramatic effect on mortality in Sapporo city[30], and eventually in the entire island of

Hokkaido[31], led to the introduction of a nationwide mass screening system for 6 month-old babies in 1985.

Later analysis of the early Japanese data as well as more recent experience and reports from Japan have tempered the early enthusiasm. Epidemiologic analysis showed that the incidence of neuroblastoma has at least doubled since the beginning of screening in Sapporo city, with an unchanged incidence in the unscreened area. Importantly, there has been no significant change in the number of diagnoses in older children[32–34], which suggests that mass screening possibly identifies tumors that would either never have presented clinically, or would have regressed spontaneously. None of the Japanese programs are population-based. Many authors affirm the central importance of studying population-based incidence and mortality rates, comparing screened and unscreened populations[32,33,35], in the evaluation of a screening program.

Moreover, several reviews of the biology of neuroblastoma detected through mass screening programs provide strong evidence that almost all of the tumors had favorable biologic features, and would therefore have conferred a very good prognosis[36,37] even if detected clinically at a later age. Children bearing such favorable tumors may therefore be overtreated[38]. On the other hand, advanced stage disease occurring in older children has persisted at a stable rate, with a dismal prognosis. It is unclear if screening at a later age[39,40] would influence the outcome of these patients since the pre-clinical stage of their tumor and the duration of the pre-clinical period are unknown. Finally, the overall decrease in mortality from neuroblastoma in Japan from the prescreening to the postscreening era simply parallels a generalized phenomenon also noted in other countries without screening programs[41]. In conclusion, although the Japanese are well recognized for their pioneering work in neuroblastoma screening[35], the lack of controlled population-based studies precludes any conclusion regarding the effect of screening on mortality rate from this disease.

The Quebec Neuroblastoma Screening Project (QNS) was initiated in 1989 to study the impact of screening a large birth cohort of infants on the population-based mortality from this tumor, comparing population-based incidence and mortality rates with 4 other prospective control populations (the states of Minnesota and Florida, the Greater Delaware Valley, and the province of Ontario) and with retrospective data[2] from the Greater Delaware Valley and the province of Quebec (prescreening data). This screening study was introduced after several preliminary and feasibility studies[42–44], as well as statistical calculations concerning the size of a study required to demonstrate a significant benefit of screening. Screening was offered at 3 weeks and at 6 months of age. As a first step, a semi-quantitative thin-layer chromatography analysis[45] was performed in Sherbrooke, with borderline or abnormal samples sent to Minneapolis

for a quantitative test using capillary-gas chromatography and mass spectroscopy (GC-MS)[46]. If the urinary excretion of VMA or HVA was elevated by GC-MS, a second urine sample was requested. Children with confirmed abnormal results were referred to one of four Quebec pediatric cancer centers for clinical and radiologic evaluation, as well as a repeat test for VMA and HVA. Children found to have disease were uniformly staged and treated according to the contemporary Pediatric Oncology Group (POG) protocols.

QNS – results

All children born between May 1, 1989 and April 30, 1994 in the Province of Quebec were offered urinary screening for neuroblastoma at 3 weeks and at 6 months of age. There were 470,229 births during this period of time; 430,000 samples were analysed for the 3 week screen (91% compliance) and 344,133 at 6 months (74% compliance). Overall specificity and predictive value of the combined screening techniques were 99,99% and 52% respectively. Thus, approximately half of the patients referred for evaluation after 2 positive urine screens were found to have neuroblastoma.

Through December 31, 1995 (20–80 months follow-up of the birth cohort), 123 cases of neuroblastoma were diagnosed. 45 patients were detected preclinically by screening, 18 at the 3 week screen and 27 at 6 months. The remaining patients (78 cases) were diagnosed clinically, having been missed by screening (54 cases), diagnosed before the 3 week screen (20 cases) or never screened (4 cases). Of the 54 cases missed by screening, 20 were 'non-secretors' at the time of diagnosis and 34 were catecholamine positive at diagnosis. Only 3 cases were found to be 'true false-negative', i.e. their urine tested positive by GC-MS on retrospective re-testing of the frozen stored filter paper. None of the 3 samples was extremely positive, either because of only mild elevation of the catecholamine metabolites, or because of the dilute nature of the sample obtained, as shown by a low creatinine concentration.

The screening program in the province of Quebec has created a very significant increase in the overall incidence of neuroblastoma, and more specifically in infants under 1 year of age[47]. From statistical analysis available through July 31, 1995, observed cases compared to the expected number of cases (using incidence data from the Surveillance, Epidemiology, and End Results (SEER) program of the US National Cancer Institute) results in a standardized incidence ratio (SIR) for the whole cohort of 2.17 (95% confidence interval (CI) 1.79–2.57, $P < 0.0001$)[47]. The SIR for two of the 4 control groups (Ontario and

Minnesota) with more rapid ascertainment of cases was within the expected range. The SIR for the group under the age of one was very significantly elevated in Quebec: 2.86 (95% CI 2.26–3.50) but unfortunately, cases over 1 year of age continued to be diagnosed with no decrease in the incidence compared to that expected (SIR 1.42).

The number of cases with early stage disease was much higher in Quebec compared to that in the control groups, but again no decrease was seen in the number of cases with advanced stages. In fact, the number of patients with stage 4 disease diagnosed in Quebec is greater than that seen in the normalized control groups. Table 4 shows the biologic characteristics of the tumors diagnosed both by screening and clinically. Most of the unfavorable tumors fall in the clinically detected group.

There have been 17 deaths from the 5 year cohort as of December 31, 1995, all of which were in the clinically detected group. Three patients diagnosed before the 3 week screen died of 4-S disease and the remaining 14 patients had stage 4 disease diagnosed after the age of one year except for one case (9 months) who was never screened. Table 5 shows the biologic features of tumors from the patients who died in Quebec.

There were 15 and 17 deaths in the Ontario and Minnesota control groups respectively. It is still too early to assess the effect of screening on

Table 4 Biological data from Quebec patients

Test	Preclinical	Clinical	Total
N-myc			
normal	43	58	101
amplified	0	12	12
unknown	2	7	9
awaiting	0	1	1
total	45	78	123
Shimada classification			
favorable	40	44	84
unfavorable	3	15	18
unknown	1	10	11
waiting results	1	9	10
total	45	78	123
Ploidy			
diploid	0	12	12
hyperdiploid	0	5	5
triploid	30	35	65
tetraploid	1	5	6
pentaploid	1	2	3
mixed aneuploid	8	9	17
diploid/aneuploid	3	5	8
hypodiploid	1	1	2
unknown	1	3	4
waiting results	0	1	1
total	45	78	123

Table 5 Neuroblastoma deaths in Quebec

Patient	Stage	Age (months)	*N-myc* copy	Ploidy	Histology
J 35	4-S	2	1	1,52	NA
L 17	4-S	1	1	1,18/1,32	U
J 90	4-S	0.5	Ampl.	1,00	NA
J 39	4	24	1	2,16	U
J 66	4	31	NA	1,33	NA
L 21	4	22	Ampl.	1,00	U
J 84	4	44	1	1,17	NA
S 11	4	24	NA	NA	NA
J 86	4	36	Ampl.	1,00	NA
J 87	4	21	Ampl.	1,68/1,95	U
J 95	4	53	1	1.64	NA
M 17	4	9	Ampl.	1.00	NA
M 27	4	15	1	1.00	F
M 19	4	12	NA	1.00	U
M 25	4	13	Ampl.	1.34	U
L 22	4	29	Ampl.	1.64	U
J 102	4	21	Ampl.	0.96	NA

F, favorable; U, unfavorable; NA, not available; Ampl., amplified

mortality from the Quebec study, but based on the available incidence data, it is very unlikely that the mortality rate will be decreased compared to the control groups by the screening program in infants. Moreover, it is unlikely that screening at an older age (> 12 months) would be feasible. At least 2 million children would have to be screened in order to show any influence on mortality from screening[48].

Conclusion

Considerable progress has been made recently in understanding human neuroblastoma. Based on our current knowledge of both the clinical and the biologic prognostic features of this tumor, several distinct categories of patients can be identified, allowing for more specific risk-related therapy. Unfortunately, patients older than 1 year of age, and patients with unfavorable tumor biology still have a poor prognosis despite very intensive therapy. It seems clear that screening for neuroblastoma in infancy does not decrease the incidence of advanced stage disease at an older age. Moreover the early detection of biologically unfavorable disease may not improve its ultimate outcome.

Future research may still improve our understanding of the underlying genetic changes of this tumor, hopefully leading to the development of

new approaches in the diagnosis and tumor-specific therapy of neuroblastoma.

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