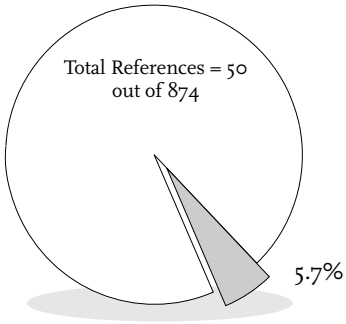
7. Remission of Neuroblastoma

Remission of Neuroblastoma



References in Chapter Seven = 50
References in Part One = 874

Neuroblastoma is a childhood tumor derived from primitive sympathetic nervous system cells. It usually occurs in the medulla of the adrenal gland, but can arise anywhere in the sympathetic nervous system. It is believed that the tumor arises during fetal development.

Estimates regarding the incidence of neuroblastoma vary. C.I.V. Franklin† gives the incidence of neuroblastoma as 1 in 100,000. Sutow et al.†† estimate its incidence as 3 per million. Robert Bolande* believes that neuroblastoma is the most common tumor to occur in newborns and young infants and estimates its incidence at 62.7 per million in infants under 1 year of age and 19.7 per million in infants under 1 month of age. The survival rates in children with neuroblastoma are much better in those cases where the malignancy is detected before 1 year of age. The relative five-year survival rates for neuroblastoma for the years 1960-86 are reported in Table One.

In a review by Audrey Evans et al.** of 174 cases of neuroblastoma, 13 cases of spontaneous regression were observed, a regression rate of 8%. In children under 6 months of age regression occurred in 15% of these 13 cases.

Chapter 7 contains 50 references, 23 of which are annotated with summaries. Some annotated references also contain 1 or more case reports. Twenty-seven supplemental references are also included as additional documentation. Full text of 30 case reports is presented (11.6% of the 258 case reports in Part One). In 13 cases in this chapter, regression occurred after the administration of massive doses of vitamin B12. Twenty-two of the cases in this chapter presented with disease under 6 months of age, 5 cases between 6 months and 1 year of age, and 2 cases over 1 year of age.

In this volume, neuroblastoma is the second most frequently reported type of cancer to undergo spontaneous regression, in agreement with Everson and Cole who, in their 1966 review, Spontaneous Regression of Cancer, reported the same finding. Only cases of renal cancer are reported with higher frequency.

A comparative analysis of cases reported in previous literature reviews is presented in Table Two.

Table One: Five-Year Relative Survival Trends for Neuroblastoma in Children Under Age 15

Years of Diagnosis	Children Under Age 15
1960-1963	25.0%
1970-1973	40.0%
1974-1976	48.6%
1977-1980	52.3%
1981-1986	56.4%

Table Two: Comparison Between Other Major Literature Reviews of Cases of Spontaneous Regression of Neuroblastoma

Tumor Site	Rohdenburg (1918) (N =185)	Fauvet (1960) (N=192)	Boyd (1966) (N=97)	Everson (1966) (N=182)	Challis (1990) (N=505)
Neuroblastoma	0	17	15	29	42

• adapted from Cancer Statistics Review 1973-1987, Lynn A. Gloeckler Ries, Benjamin F. Hankey, and Brenda K. Edwards, editors, published by U. S. Department of Health and Human Services, IV. 6.

† C.I.V. Franklin, Prolonged Arrest of Cancer [Chichester, England: John Wiley & Sons Ltd] 1982, 103-116.

†† W.W. Sutow, T.J. Vietti and D.I. Fernback, Clinical Pediatric Oncology [Mosby: St. Louis] 1973, 2.

* Robert P. Bolande, "Spontaneous Regression and Cytodifferentiation of Cancer in Early Life: The Oncogenic Grace Period," Survey and Synthetics of Pathology Research 4: 1985, 296-311.

** Audrey E. Evans, James Gerson and Louise Schnaufer, "Spontaneous Regression of Neuroblastoma," NCI Monograph 44: 1976, 49-54.

Neuroblastoma

Preliminary Observations on the Treatment of Neuroblastoma with Vitamin B12

Bodian M

British Empire Cancer Campaign 31: 1953; 174-179

Extracted Summary

Ten cases are reported in which vitamin B12 is used in the treatment of neuroblastoma alone or in combination with other treatment procedures.

The author discusses the ways in which recovery from neuroblastoma might occur as theorized by Farber (American Journal of Diseases in Children 60 (1940) 749): (a) the neuroblastoma may undergo spontaneous hemorrhage and necrosis and disappear without any treatment; (b) the neuroblastoma may undergo spontaneous maturation or metaplasia (sic) and become a benign ganglioneuroma; (c) the neuroblastoma may be treated successfully by a combination of surgical removal of the tumor followed by irradiation.

The author suggests that possible modes of action of vitamin B12 on neuroblastoma include direct metabolic interference or by induction of growth that exceeds the available nutrients, hence promoting a necrotizing process.

Selected Case Report

Case 1: A massive pelvic neuroblastoma of poor differentiation underwent virtually complete regression, and the patient is now in good health 3 years after the onset of symptoms. At no time during the course of the disease was there clinical or radiological evidence of metastasis. Regression occurred during the early months of treatment with vitamin B12, and no other therapy was employed.

I Simpatoblastomi

Antoniazzi B

Tumori 40: 1954; 667-676

Extracted Summary

The histo-anatomical and clinico-radiological characteristics of sympathoblastomas are shortly reviewed and some particular possibilities of evolution are pointed out. Two of author's own cases illustrating peculiar clinical aspects and evolution of the disease are presented.

Selected Case Report

The second case regards a two-year-old girl, with a swelling on the right side of her head that slowly grew reaching the volume of a tangerine. This swelling was lymphoglandular covered by unbroken skin with a hard consistency. The radiological examination of the thorax demonstrated the presence of a roundish, intensely opaque and homogeneous formation with a well-defined profile occupying the apical right infero-clavicular region. It touched the trachea medially, pushing it to the left. In the lateral projection, this formation was localized in the medial posterior levels of the lungs.

A biopsy of a lymph gland on the right side of the head was performed. The histological examination (Prof. Sirtori) stated: "the newly formed tissue has almost completely replaced the glandular lymphatic tissue. It is made up of diamond-shaped formations with lymphoblast and histiocyte-type cells whose cytoplasmic extensions collect at the center of the formations or get lost in a fine reticular woof that constitutes a common base to the whole tumor and that corresponds to fine amyelinic fibers. The areas of necrosis and hemorrhage are extensive." The histological diagnosis was sympathoblastoma.

Six months later, without any treatment, the lymphoglandular formation seated laterally on the head had completely disappeared while the endothoracic tumor was greatly reduced. After more than two years from

the first observation, the girl was well. No ganglia could be observed. The endothoracic swelling was very reduced in volume and a sickle-shaped calcification could be observed within it.

In our opinion this sympathoblastoma arising in the thorax with metastatic localizations and lymphoglands situated on the side of the head regressed spontaneously. From the histological point of view we should point out that there were areas of necrosis and hemorrhaging which extended progressively toward the center of the tumor and might have contributed, as we mentioned earlier, to its regression. The report of a calcification within the context of the endothoracical tumoral mass, which was also reduced in volume, confirms this evolution.

(Noetic Sciences translation)

The Treatment of Neuroblastoma with Vitamin B12

Bodian M

British Empire Cancer Campaign 32: 1954; 199-202

Extracted Summary

In the 31st Report preliminary observations were made on the effects of vitamin B12 in 10 children with neuroblastoma. All of the cases alive at the time of that report have subsequently been followed up and remain in good health without evidence of active disease, with the single exception of Case 2. Nine further children with verified neuroblastoma have been treated since the previous report was issued, and are reported in this review. (Cases 11-19)

Selected Case Reports

Case 16 was admitted at the age of 10 months because of paresis of the legs since birth. There was evidence of sphincter paralysis. A portion of the extradural fat was removed at laminectomy and found to contain both neuroblastic and neurofibromatous tissue. Laparotomy revealed a small para-vertebral tumour which was excised and proved to be of similar structure. Vitamin B12 therapy was commenced subsequently, and when the child was last seen 3 months later she was beginning to stand up on her own.

Case 17 presented elsewhere at the age of 10 months with jaundice and was found to have a massive inoperable retroperitoneal tumour. Cholecystjejunostomy was undertaken, and a biopsy showed that the growth was a neuroblastoma. After operation she remained ill and suffered recurrent jaundice. The patient was admitted to this Hospital 3 months after operation, in a slightly improved state of health. There was slight anaemia, but no radiological evidence of skeletal metastases. At the present time, a year from initial presentation and over 8 months after the commencement of treatment with vitamin B12, the child is in excellent health and free from jaundice, and the abdominal tumour considerably smaller in size.

Case 18 suffered from progressive signs of spinal cord compression from the age of 4 months, and was admitted to the Beilinson Hospital, Israel, 5 months later with flaccid paraplegia and an abdominal mass, biopsy of which yielded neuroblastic tissue. Radiography revealed that the tumour extended into the spinal canal. At this Hospital the intraspinal portion was found to be irremovable, and only a biopsy was taken. Within a month of commencing vitamin B12 therapy there was definite increase of muscular power in the legs, and there has been further improvement up to the present time, a year from clinical onset.

Neuroblastoma and Vitamin B12 Therapy

Bodian M

British Empire Cancer Campaign 33: 1955; 186-188

Extracted Summary

In two previous reports (1953, 1954) we have reviewed a series of 19 cases of neuroblastoma treated with massive doses of Vitamin B12.

The standard mode of therapy used has consisted of intramuscular injections, each of 1,000 micrograms on alternate days, the course being maintained for from 2 to 2 1/2 years where survival permitted.

Since our last report three of the patients reported (Cases 2, 15, 17) have died with a recrudescence of the disease and widespread dissemination of metastases, at intervals of 32, 18 and 21

months respectively from the onset of symptoms. A further group of eight children with verified neuroblastoma has been treated with Vitamin B12; one of these is excluded from the survey as he died within a month from the commencement of treatment, and two others have only recently come under observation. Abstracts of the remaining five cases are given.

Selected Case Report

Case 24: A female infant who was admitted within three hours of birth because of abdominal swelling. On examination there was gross enlargement of the liver, which extended down to the right iliac fossa. At laparotomy the entire liver was slightly lobular, and biopsy revealed extensive replacement by neuroblastic tissue showing slight differentiation. Vitamin B12 therapy was commenced and there has been a progressive and marked reduction in the size of the liver, the child being in good general health and free from further evidence of metastases at the age of 6 months.

The Treatment of Neuroblastoma with Vitamin B12

Bodian M

British Empire Cancer Campaign 34: 1956; 213-216

Extracted Summary

In 1951, massive Vitamin B12 therapy was given to a patient with neuroblastoma at this hospital, with the idea that this agent might enhance the maturation of the neoplastic cells and bring about the conversion of the growth to a benign ganglioneuroma. During the course of treatment, however, a remarkable regression of the massive pelvic tumour occurred, leading eventually to its complete disappearance. Since that time, a further 27 patients with histologically verified neuroblastoma have been treated with Vitamin B12. None of these patients has been denied treatment by conventional methods (surgery and radiotherapy), but in many instances such factors as the extent or location of the primary tumour, and/or the presence of obvious metastases, have precluded their use. For such reasons the majority of the cases treated with Vitamin B12 have been "selected" because no other mode of therapy offered any prospect of arresting the disease. Summaries of Cases 25-30 which have not been included in previous issues of this Report are included.

Selected Case Report

Case 30: A male infant admitted at 3 weeks of age with flaccid paralysis of legs and an abdominal swelling, both apparent from birth. X-ray examination and surgical exploration revealed a dumb-bell tumour, and biopsy showed this to be a neuroblastoma. After Vitamin B12 therapy for 7 months the child continues to make good progress, though the paralysis is unrelieved.

The Problem of Spontaneous Regressions of Malignant Tumors

Sirtori C; Pizzetti R

Giornale Italiano di Chemioterapia 3: 1956; 176-199

Extracted Summary

A critical review is made of the cases of spontaneous regression of malignant tumours referred in the literature. Three personal cases are described, concerning: a) a 2-year-old baby with large laterocervical metastases of mediastinic neuroblastoma, spontaneously regressed for five years; b) a baby of few months, with laterocervical metastases of neuroblastoma (the site of the primary tumor not discovered) spontaneously regressed for 4 years; c) a 26-year-old woman, hysterectomized for chorioepithelioma, with pulmonary, vaginal and subcutaneous metastases, regressed for 7 years.

Spontaneous regressions may be related to ischemic necrosis, to cellular differentiation or to a defensive action of the stroma. A comparison is made between the cytohistological features of the spontaneous and therapeutical regressions: the former show cytolysis, differentiation and connectival reactions, in the latter are more typical the mitotic alterations.

Spontaneous healing may be biologically related to endocrine or neurohormonal factors, to general or local immunity phenomena, to sudden variations of the biological balance of the soma, and to other yet unknown stimulations.

False regressions concern the cases of erroneous diagnosis, some tumours of biologically doubtful malignancy (Smith's multiple cutaneous epithelioma, papillary tumours of the ovary), and finally tumours that easily undergo noticeable clinical regressions (hypernephroma).

A regression may be simulated also in the cases in which metastases or relapses appear after a very long period of latency. Two interesting personal observations are referred, concerning: a) a lymphogranuloma which remained clinically completely silent during 6 years in a young woman, allowing marriage and a normal delivery; b) an ovarian adenocarcinoma, which gave clinical evidence of pulmonary metastases (operated) 26 years after the ovariectomy.

Further studies of the spontaneous regressions of cancer will be useful to understand the great differences of malignancy existing in a same type of tumour, the intrinsic defence powers of some organisms, the biochemical and morphological features of such a defence and the exact mechanism of action of some anticancer substances.

Selected Case Reports

A first case which has been published (Sirtori, Rock, Veronesi) regards a 2-year-old girl with right laterocervical adenomegaly with mediastinic mass as large as an orange and occupying the upper third of the ipsilateral hemithorax. Biopsy revealed lymphoglandular metastases of neuroblastoma. Left without specific treatment, the girl recovered spontaneously and after 6 years the laterocervical glands could no longer be palpated and the mediastinic mass had practically disappeared.

A second case regards an infant affected by laterocervical adenopathy. After biopsy, a histologist diagnosed lymphosarcoma, but a successive check-up revealed the neuroblastoma-like nature of the lymphoglandular metastases. The father of the boy, who was an M.D. and was aware of the possibility of spontaneous regression, did not want his son to undergo any therapy. In fact, the lymph glands regressed and after two years a biopsy performed on one of the glands revealed an ample cytolysis of the tumor. There was complete regression of the laterocervical masses within 4 years from the beginning of the disease. (Noetic Sciences translation)

The Treatment of Neuroblastoma with Vitamin B12

Bodian M

British Empire Cancer Campaign 35(2): 1957; 227-230

Extracted Summary

An annual survey of an investigation into the response of neuroblastoma to massive Vitamin B12 therapy has been provided in the Annual Reports from 1953 to 1956 inclusive. In the last issue the entire series was reviewed covering twenty-eight children where treatment was commenced between January 1951 and June 1956. Of this total, fifteen patients had shown evidence of tumour regression, and ten were alive in remission at intervals from 7 months to 6 years from the commencement of treatment. One further child had succumbed to an intercurrent infection (poliomyelitis) and was then found to be free from tumour at autopsy. Regression in the remaining four children was of a temporary nature. Up to June 1957 treatment has been extended to include a further eight patients with neuroblastoma. Case summaries of Cases 31-38 are included.

Neuroblastoma: A Roentgenologic and Pathologic Study

Kincaid OW; Hodgson JR; Dockerty MB
American Journal of Roentgenology 78: Sept 1957; 420-436

Extracted Summary

The clinical records and pathologic material were reviewed on 32 histologically proved cases of neuroblastoma seen at the Mayo Clinic in the ten-year period through 1954. The roentgenograms of these patients were carefully studied in an attempt to establish criteria for the roentgenologic diagnosis of this disease.

Certain roentgenologic findings or combinations of findings are specific for neuroblastoma: (1) abdominal or thoracic paravertebral masses with evidence of calcification; (2) bilateral symmetry of skeletal lesions where skeletal metastases exist; (3) a predominance of mixed destructive and proliferative bone changes; (4) frequent cortical destruction; (5) occasional extension into adjacent soft tissues; and (6) the presence of a pathological fracture. In many instances the diagnosis can be made by the roentgenologist with a high degree of accuracy.

A striking feature of the natural history of neuroblastoma is the reported tendency of the tumor in some cases to regress spontaneously and to undergo transformation into benign ganglioneuroma. Several such cases have been reported in the literature and seem well-authenticated.

Neuroblastoma

Bodian M
Pediatric Clinics of North America 6: 1959; 449-472

Extracted Summary

A study of the natural history of neuroblastoma was based on an analysis of 58 untreated cases, and this information was used as a background to the evaluation of (1) local forms of treatment, i.e., surgery and/or radiotherapy, and (2) a systematised form of treatment, namely, massive doses of vitamin B12 with or without surgery and/or radiotherapy. The single most important prognostic factor was found to be the age at symptomatic onset of the disease, the critical division being less than or over the age of one year.

This biological difference was not overt in the untreated group, which included 20 infants under 1 year. Only 1 of these survived, the sole instance of complete spontaneous regression among the 129 children in the whole series. The average period of survival among the 19 fatal cases in infancy was merely 3 months.

The conventionally treated group of 25 children included 9 infants, five of whom, all without any evidence of metastases, survived. Of the four fatal cases, three showed evidence of secondary spread, and the average survival period among the fatal cases in this group was 8 1/2 months. Survival seemed to be of a high order when onset in infancy was coupled with absence of metastases.

Of the vitamin B12-treated group of 46 children, 4 were not evaluated, owing to their follow-up period being less than 1 year. Of the 42 remaining children, 17 manifested the disease in infancy, and all of these showed clinical remission, in spite of secondary spread, except to the skeleton, in all but 4 instances. Maintained remission for periods of 1 to 8 years in 13, complete regression of tumour in a child succumbing to poliomyelitis, and temporary remission with ultimate recurrence of disease and fatal issue in 3 further cases is the score at present. The average period of survival among the 4 fatal cases with onset in infancy in this group was 19 months. Remission of tumour in the age group over 1 year was much less common; it was observed in 5 of the 25 cases so defined.

Neuroblastoma Sympatheticum

A Study and Report of 217 Cases

Gross RE; Farber S; Martin LW

Pediatrics 23(6): June 1959; 1179-1191

Extracted Summary

The treatment of patients with neuroblastoma does not lie solely in the province of a single specialty; it requires cooperation of pediatrician, surgeon, radiologist and tumor therapist. It is essential that they all be aware of the unique characteristics of this particular tumor if optimum results are to be obtained. The many factors found to influence the prognosis for a child with neuroblastoma are discussed.

Prior to the authors' adoption of x-ray therapy as a part of the treatment of neuroblastomas (about 1937), 20 patients with neuroblastoma had only biopsy and were not given any definitive therapy: all were found to be inoperable. Two infants regarded as hopeless at the time, because of widespread and nonremovable neoplasm, are now well and completely free of disease 20 and 25 years later. Presumably, the very cellular and rapidly expanding tumor grew beyond its blood supply, then degenerated and disappeared. Possibly, there are some poorly understood antibody reactions between host and tumor, leading in some cases to dissolution of the latter. Suffice it to say that there are a few well-documented cases wherein neuroblastoma has disappeared completely and permanently.

We have seen two patients who undoubtedly represent spontaneous cures. These were among patients seen during the early part of the series, and both were regarded as inoperable. In one, a 6-week-old infant, at surgery there was a large tumor arising out of the pelvis. Biopsy showed neuroblastoma. No treatment was given. Subsequently, the abdominal mass gradually disappeared. This individual was completely asymptomatic and in robust health when examined 25 years later. The other was an 11-month-old infant with a large tumor arising from the posterior mediastinum; biopsy showed neuroblastoma. No treatment was given. She was asymptomatic, with a normal roentgenogram of the chest 20 years later.

In two other instances, we have encountered, at surgery, a large primary tumor of the suprarenal area with much neoplasm in the regional lymph nodes. Histologically, in each instance, both the main tumor and the smaller tumors in lymph nodes were completely benign ganglioneuromas. We suspect that these tumors were originally malignant neuroblastomas and that the primary tumor and the metastases to lymph nodes had undergone maturation into benign ganglioneuromas. Because of uncertainty, these two cases have not been included in the series in the present report. In general, spontaneous cure may be expected to occur in a very small percentage of cases of neuroblastoma.

Problems in the Prognosis of Neuroblastoma

Dargeon HW

American Journal of Roentgenology 83(3): March 1960; 551-555

Extracted Summary

A review of 180 cases of neuroblastoma reported at the Pediatric Service of Memorial Hospital for Cancer and Allied Diseases between 1926 and 1958 is presented. It seems evident that the natural history of neuroblastoma may vary greatly from child to child. Surgery and irradiation are the recognized therapeutic modalities. Chemotherapy is still of questionable value but investigation of its effects should be continued. The prognostic evaluation must be guarded, for, as in other cancers, the five-year, ten-year or longer survival "yardsticks" may prove erroneous in some instances.

One of the cases presented is that of a child with biopsied neuroblastoma who underwent a spontaneous remission with no treatment.

Selected Case Report

In 1956, a female child aged four months was admitted with multiple subcutaneous nodules, one of which was biopsied and showed neuroblastoma, and a very enlarged liver. The family refused any therapy and took her home against advice. Six months later the nodules began to disappear and in December 1958, at the age of two and one half years, she shows no signs of disease. At present this would be called a spontaneous clinical remission but we do not know whether reactivation of the recognized sites or growth of possible unrecognized sites may subsequently occur.

Cutaneously Metastasizing Sympathetic Neuroblastoma with "Spontaneous" Regression

Hornstein VO; Mülke G

Dermatologica 120: 1960; 35-52

Extracted Summary

An infant, age three weeks, is described. Without any effect on the general health there were numerous cutaneous metastases secondary to a sympathetic neuroblastoma of the right suprarenal gland. Radiotherapy of one of the cutaneous lesions and the administration of corticosteroids had no effect. At the age of 6 months all the tumours disappeared rapidly. After more than 2 years there has been no relapse. The regression of the tumours coincided with an attack of chickenpox and the authors discuss the possibility of the virus having an oncolytic effect.

Selected Case Report

In August 1957, a 7-week-old, 4,500 gram heavy eutrophic female infant was admitted to the University Children's Clinic in Wuerzburg. Her mother had noticed small nodes under the skin around both hips and the genitals when the child was 2 or 3 weeks old. There had been no unusual occurrences during pregnancy and birth. Weight at birth: 3,300 grams. She was the second child of healthy parents. During early infancy she had had thrush of the oral cavity. Apart from that there had not been any serious disease, and the child had developed well with breast-feeding.

Findings at admission (August 21, 1957): The body stem and the proximal parts of the lower extremities showed many deep-cutaneous to subcutaneous tumours ranging in size from bean size to pigeon-egg size, of sturdy consistency. They were mainly easily moveable, partly a bit stuck to the covering skin and obviously painless upon pressure. The covering skin was moderately tight and reddened in many places. Apart from that there were no pathological findings on the well-developed infant. In particular palpable tumours of the liver or the spleen were missing. Neither did palpation reveal enlarged lymph nodes under the skin. Peripheral blood picture, erythrocyte sedimentation rate, punctate of the bone marrow, bacteriological blood culture, WaR and side reactions, stool, urine, all x-ray examinations (skeleton and mediastinum) were without pathological findings. The tuberculin reaction according to Moro was negative.

The child was presented in the University Skin Clinic. A single tumour was excised for histological examination. The histological findings (No. 755/57) were: Epidermis and skin appendages without findings. The lower corium and the adjacent adipose tissue contained numerous nests and cords of undifferentiated tumourous tissue of relatively microcellular lymphocytoid to monocytoid structure. There is a clear tendency to infiltration. The tightly packed cell elements mainly have a low content of cytoplasm, at times it was almost the bare nucleus only. They differed only slightly in the shape of nucleus and size. Sporadic karyokineses, including pathological forms and distinctive nuclear mitoses are repeatedly found. No typical development of pseudorosettes, however, small patches of fine filaceous, faintly basophil material, often coronally surrounded by tumourous cells. Silver impregnation according to Goemoeri didn't reveal reticulum-fibrils of the tumour. Some slight metachromasia of the connecting tissue of the stroma.

Histological diagnosis: Obviously metastasis of a microcellular neurogenic tumour, most probably of a sympathetic neuroblastoma. No certain evidence for reticulosis or any other systemic disease of the reticuloendothelial system. Based on the unexpected diagnosis, which clearly contradicted the infant's good health condition, and therefore met with considerable scepticism, new x-rays of the abdomen were taken. For the time being no pathological changes could be discovered.

Prednisone was administered (10 milligrams per os for 2 weeks) and an x-ray irradiation of a metastasis on the right thigh was performed (in total 6 x 400 roentgens in 5 weeks) without any influence. On the other hand the child's general condition remained good (apart from a slight anemia), while even more tumours were growing under the skin. A new trial excision and histological examination in the University Skin Clinic resulted in the

same tumour diagnosis. Now, however, a certain reproduction and spreading of the filaceous-mucoid, however, not metachromic focuses found in the first excision. Some cell-nests were literally intercalcified. Moreover necrosis and calcium incrustation were sporadically recognizable.

A repeat x-ray examination now revealed numerous calcifications around the right suprarenal gland, so that this had to be regarded as the location of the primary tumour. Retrospectively the first x-rays also showed traces of calcareous intercalation in the same area, which, however, had not been detectable due to a strong interference.

For a while the further course was marked only by persistent pyoderma and some feeding disturbances, without any remarkable deterioration of the child's general condition or even a cachexia of the tumours.

At the age of 5 1/2 months the child suffered from chickenpox. Since that time the skin tumours shrank remarkably! At the age of 6 1/2 months many of the small nodes, especially the ones which had developed last, had already disappeared. During all that time the child had been observed only, but had not received any medical treatment.

In January 1958, a third histological examination was carried out in the University Skin Clinic which presented a completely changed picture: Unclearly localized nests without any signs of tumourous proliferation, however, showing regressive changes. These were hyaline-amorph or fine-filaceous, irregularly spread, moderately basophil powdered focuses, reminiscent of tissue coagulum or "neurohyalin." These were partly without cells or surrounded by poorly dyeable marginal cell elements.

Also within these degenerating focuses some sparse "fading" cell elements were found. A patch of lymph histocytical inflammation with single giant cells of foreign body type was located in the surrounding connective tissue of the stroma. Based on these findings, the original histological diagnosis of neuroblastoma would not have been possible any more. The consistency of the steadily shrinking tumours became more and more inhomogeneous. X-rays often revealed small calcification focuses.

In the meantime only very sparse remains of tumours are there, on the back of the neck, the outside left thigh and in the left labium majus pudendi, as hard as stone. Under certain incidence of light some rough structure of the skin becomes visible on the back and the front of the body where the tumours were located. Apart from that our little patient, who is 2 1/2 years old now, is very healthy and is neither physically nor mentally retarded.

(Noetic Sciences translation)

Neuroblastoma

Review of Twenty-Eight Cases and Presentation of Two Cases with Metastases and Long Survival

King RL; Storaasli JP; Bolande RP

American Journal of Roentgenology 85(4): April 1961; 733-747

Extracted Summary

A review of the course and therapy of 28 cases of neuroblastoma has been presented, with a two-year survival of 50% recorded in 26 patients. The treatment of choice is complete surgical removal of the tumor followed by radiation therapy to the tumor bed. Radiation therapy is useful for the treatment of metastatic disease.

Our data seem to indicate that the site of origin of the tumor may be the most important prognostic factor. In this series, only 1 patient out of 10 is surviving whose primary tumor was in the adrenal gland, while all patients with extra-adrenal primary sites have survived. In addition, the presence of metastases and the histologic characteristics of the tumor are of prognostic importance.

Two cases with metastatic disease and long-term survival are presented.

Selected Case Report

Case 2: D.H., a three-day-old white male, was admitted to the hospital with an enlarged liver and spleen. A nodular mass was felt in the skin overlying the right scapula, and another smaller mass over the right anterior chest. The liver was enlarged 4 centimeters and the spleen 5 centimeters below the costal margin. On August 23, 1952 a biopsy of the left tibial marrow was not diagnostic, but a biopsy of the left scapular skin nodule revealed a very anaplastic tumor consistent with the diagnosis of a sympathicoblastoma. A primary site was never found. The patient was discharged from the hospital with no specific therapy and a grave prognosis.

He was seen in the clinic on September 5, 1952 at which time there were many more nodules present in the skin, involving the entire body, varying in size from several millimeters to a centimeter. The hepatomegaly and splenomegaly persisted. The patient was, however, eating well and gaining weight. He was next seen on October 24, 1952, at which time the skin nodules were decreasing in size and number. During the next four months all of the nodules disappeared, and the liver and spleen returned to normal size, and the infant appeared healthy. He has had no further difficulty and is living and well at the present time.

Neuroblastoma

Dargeon HW
Journal of Pediatrics 61: 1962; 456

Extracted Summary

The frequency with which childhood cancers are observed increases annually. In the experience of the Pediatric Department of Memorial Hospital for Cancer and Allied Diseases neuroblastoma is foremost in incidence among the solid malignant tumors that occur in children. This review of 236 cases emphasizes features of clinical significance in diagnosis, therapy, and prognosis. The diagnosis is quite readily made in some instances, while in others it may present insurmountable difficulties. Plans for treatment require considerations regarding the site, or in metastatic cases sites, the operability of the tumor, and the use of pre- or postoperative irradiation and chemotherapy. The method of management must often be altered by the problems encountered in the individual case. There is now a larger number of survivors and metastatic disease does not always indicate a fatal prognosis. Recognition of the not infrequent bizarre clinical course, at times resulting in even 'spontaneous' arrest, makes caution in the appraisal of therapeutic successes mandatory.

Spontaneous Disappearance of Neuroblastoma with Maturation to Ganglioneuroma

Eyre-Brook AL; Hewer TF
Journal of Bone and Joint Surgery (Great Britain) 44-B(4): Nov 1962; 886-890

Extracted Summary

A three-month-old girl presented with a massive abdominal tumour arising from the right lumbar region. Microscopic examination of a biopsy specimen showed a typical neuroblastoma. No treatment was given except that necessary symptomatically for paralysis caused by compression of the cauda equina. Spontaneous regression was accompanied by maturation to a small ganglioneuroma found at necropsy examination at the age of ten years. Death was from urinary infection due to a persistent neurogenic bladder.

Selected Case Report

The patient was a girl born on June 6, 1949. At the age of three months the child was noted to have a hard swelling in the right lumbar muscles. Within a further month there was weakness in the left calf muscles and the lumbar swelling had grown. An abdominal swelling on the left side was readily palpated within a further four weeks, and the child was admitted to hospital at the age of five months. At that time there was a mass below and to the left of the umbilicus and a firm ovoid mass about an inch and a half in length in the right lumbar region. This appeared to be inseparable from the muscles and just to the side of the spine. The skin over the lump was reddened. The left leg was flexed and abducted at the hip and fixed at the knee, and there was a marked foot drop. There was no movement of the foot but slight power of extension of the knee. In the right lower limb there was no movement of the foot but normal control of the knee and hip. The urine contained pus cells and coliform bacilli.

Radiographic examination (November 1949) showed a soft-tissue mass in the pelvis and right side of the abdomen, with calcification in the right side of the pelvic cavity. There was no lung or mediastinal lesion. Intravenous pyelography showed that the right kidney was high but probably normal. The left kidney was "full" with stasis in the left ureter. The bladder was deformed by an extrinsic mass lying mainly to its right side and above it. No abnormality was shown in the limbs.

Biopsy (December 1949): A biopsy was performed by Mr. W. A. Jackman. Through an incision parallel to the right iliac crest at the level of the third lumbar spinous process a hard grey lobulated mass was exposed. The tumour was adherent to the iliac crest and surrounding structures and extended anteriorly. A large piece was removed for examination.

The tumour was lobulated and on section showed a white cellular appearance with areas of haemorrhage. Microscopically it was composed of masses and cords of small cells with scanty cytoplasm and darkly staining round or oval nuclei. The cells had a tendency to be arranged around circular spaces containing radiating

fibrils derived from the cellular cytoplasm, the classical rosettes of a neuroblastoma. The tumour was more highly differentiated than many neuroblastomata seen at this age, in that the rosettes were numerous, but there were no ganglion cells. Treatment was thought unlikely to benefit the child, and she was allowed to go home.

Progress: She was next seen a year later when she was admitted in good general health apart from deformity of the feet and some urinary retention with overflow, and consequent cystitis. The mass was no longer clearly felt, and the abdomen much less distended; in fact the presence of any residual tumour was in doubt. There was no sign of metastases, visceral or skeletal. During the next eight and a half years the child was admitted on twelve occasions for treatment of the paralysis of the legs and the impaired bladder function, which led to progressive deterioration in kidney function. The child eventually died in June 1959 from uraemia at the age of ten years. Only a limited necropsy was performed. The abdomen showed no abnormality apart from gross pyonephrosis and dilation of the bladder and ureters. The lumbar spine and sacrum were removed for detailed examination. The chest and skull were not opened.

Pathology of the Specimen: The specimen consisted of the whole lumbar spine with sacrum attached. The nerve roots were exposed opposite the lower four lumbar vertebrae by cutting away the laminae and the lateral masses. The spinal theca in the region of the third and fourth lumbar nerves was thickened, and on the right side there was a layer of tough fibrous tissue densely attached to the theca and extending out over both lumbar nerve roots. This material was not bulky and had not invaded the bone of the intervertebral canal. There was no similar tissue on the left side. The nerve roots on the left side appeared normal, as did the first and second lumbar roots on the right. The third and fourth roots, lying within their intervertebral foramina, were embedded in a mass of slightly brownish fibrous tissue. This was densely adherent to the bone but could be dissected away from it. On coronal section through these two nerve roots the nerve trunks were seen running through shiny fibrous tissue. The anterior surface of the spinal theca was densely adherent to the posterior aspect of the bodies of the third, fourth and fifth lumbar vertebrae. The theca was normal as far as the level of the fourth and fifth lumbar vertebrae, where the cauda equina was embedded in rather dense fibrous adhesions which had a slightly brownish tint. These adhesions lay under an area where the theca was thickened. There was no sign of tumour within the thickened theca. The spinal cord above this level appeared normal macroscopically.

Microscopically, sections from many different levels in the dense fibrous tissue to the right of the lumbar spine showed no sign of tumour until the area just outside the intervertebral foramina was reached. Here, in a matrix of dense collagen, was a group of abnormal ganglion cells most of which were multinucleate but without mitoses. There were no really primitive cells and consequently no rosettes. The appearance was that of a ganglioneuroma. The proportion of tumour to fibrous tissue was very low.

Microscopic examination of the lumbar spinal cord revealed an area of demyelination extending up the posterior columns on the right side. There was no invasion of the theca by tumour cells, and no fibrosis within the theca. The tissue in which calcification had been detected radiographically was not represented in the specimen, and the calcification had almost disappeared in the later radiographs.

Neuroblastoma

An Evaluation of its Natural History and the Effects of Therapy, with Particular Reference to Treatment by Massive Doses of Vitamin B12

Bodian M

Archives of Diseases in Childhood 38: 1963; 606-619

Extracted Summary

The author has collected a series of 58 children with neuroblastoma in whom no active treatment was undertaken, but it should be stressed that all these cases have been histologically confirmed, either by means of biopsy or at autopsy. The average survival period of the untreated fatal cases was four months from symptomatic onset. Among the 58 untreated children included, no less than 20 showed a symptomatic onset of the illness in the first year of life, and 19 of these succumbed to the disease, as did all the ones aged more than 1 year. The one solitary survivor in the untreated series is the only instance of spontaneous regression in our series.

In November 1950, a new treatment was introduced, Vitamin B12 injections. A completely unselected series of 82 patients with neuroblastoma was given this treatment. Of these, 33 children have been complete clinical failures; 8 children have shown temporary improvement; 8 more were

excluded because the length of treament was considered to be inadequate. Thirty-two children have been classified as clinical remissions; 30 of them are alive, 28 for periods of from more than 2 years to 12 years. Two children have died after Vitamin B12 therapy from other causes, with no evidence of tumor at autopsy.

Selected Case Reports

Untreated survivor: A 4-month-old boy presented in 1947 with a mass in the chest, a grossly enlarged liver, and a subcutaneous nodule which proved histologically to be a deposit of neuroblastoma. In the absence of any form of treatment this child is alive and in good health at present (aged 15 years), the only clinical abnormality being residual calcification on radiographs in liver and thorax.

Case 1: Male, born April 10, 1950, admitted to this hospital aged 7 months with retention of urine of recent onset. After decompression of distended bladder by suprapubic cystotomy, a large fixed presacral mass was palpable extending around rectum, almost filling pelvis and projecting upwards into left iliac fossa. Biopsy through rectal wall on two occasions showed neuroblastoma with minimal differentiation.

His general condition was poor and there was persistent urinary infection. Surgical excision of massive tumour seemed out of question. Expert opinion considered radiotherapy unlikely to be successful. Metastases not found. It was decided to give him 1 milligram vitamin B12 intramuscular on alternate days. After four months' treatment tumour no longer palpable through abdominal wall, but there was some infiltration in vicinity of prostate on rectal examination. Subsequently urine was voided per urethram and suprapubic tube was removed.

After 15 months' treatment laparotomy was performed in hope of obtaining residual ganglioneuroma. Only remnants of tumour were two minute retroperitoneal nodules on left of sacrum, that were palpable but not visible. Treatment was maintained for two years. Child now in good health and free from recurrence or metastases, 12 years after clinical onset of disease.

Case 4: Female. Born February 15, 1953, admitted at 10 months because of paralysis of legs since birth with evidence of sphincter paralysis. Laminectomy was performed. Extradural tumour found which was partially removed, and which contained both neuroblastoma and neurofibroma. Laparotomy revealed small paravertebral tumour which was excised and which showed a similar histological structure. Vitamin B12 therapy instituted and child was known to be alive and well two years and three months after commencement of treatment, when she was lost sight of. (She emigrated to Canada and could not be traced.)

Case 5: Female, presented at 4 months with weakness of both lower limbs, especially of left. Double sphincter weakness was suspected. At 9 months child was admitted to Beilinson Hospital, Israel (May 3, 1954). In left lumbar region at level of L2-3 a hard mass was palpable 'the size of an orange.' There seemed to be complete anaesthesia from L1 downwards, flaccid paralysis of right leg and almost complete paralysis of left lower limb. Radiograph showed round, calcified paravertebral mass to left of upper lumbar spine. Myelography revealed filling defect on left side of spinal canal in upper lumbar region. Laparotomy, June 8, 1954, revealed left-sided retroperitoneal tumour infiltrating muscle and extending into spinal canal through intervertebral foramina. The tumour 'the size of an egg' was considered inoperable, and only a biopsy specimen was obtained, which was examined by author and proved to be neuroblastoma with some areas showing moderate degree of differentiation. There was infiltration of adjacent skeletal muscle and necrosis and calcification. On July 7, 1954, she was admitted with gross paralysis of both lower limbs, especially the right, and sensory loss over whole of right lower limb. Spinal cord and membranes were displaced to right from L1-L5. Laminectomy from L2-L5 and dura found to be completely covered by purplish-grey firm tumour. Only a biopsy was removed and microscopy showed neuroblastoma with some calcification. Vitamin B12 (1 milligram intramuscular on alternate days) initiated on July 16, 1954. At end of September 1954, child returned to Israel with improvement in power of lower limbs. There was still incontinence. Her general health was excellent. Vitamin B12 was continued, and at end of June 1955 she was brought back here. Her condition was excellent; she had good weight increase; abdomen was not distended; tone of lower extremities still diminished, particularly on left; moderate power, better on left than right; reflexes absent, she walked on wide base using surgical boots. On skeletal survey there were no metastases. She returned to Israel in September 1955. Voluntary movement of both lower limbs had improved and tone was nearly normal. Vitamin B12 was continued and she progressed very well.

In June 1957, however, she contracted bulbar form of poliomyelitis, nearly at the end of a two years' course of vitamin B12. She succumbed within 30 hours of admission to hospital. At autopsy only a fibrous scar was found at site of former tumour, and complete regression was also established by exacting histological examination confirmed by author.

Case 8: Female, born August 1, 1955, admitted here when 3 hours old with huge nodular abdominal mass on right side extending from costal margin to inguinal ligament, and across to left flank, fixed and apparently arising from loin and indistinguishable from liver. Mass was palpable per rectum. Her general condi-

tion was good. At laparotomy on August 3, 1955, mass identified as liver showing numerous nodular neoplastic deposits. Biopsy showed massive replacement of liver parenchyma by primitive neuroblastoma, as well as infiltration of portal lymphatics with tumour. Radiologically there was no evidence of metastases to skeleton or lungs. Vitamin B12 1 milligram intramuscular, on alternate days was commenced, and continued for two and a half years as sole form of treatment. After transient increase in size of abdomen, mass was decreasing by October 1955, and by February 1956 liver edge was barely palpable, and intravenous pyelogram was normal, without calcification in suprarenal regions.

She had made uninterrupted progress, and is perfectly well without evidence of recurrence of tumour at 7 1/2 years. Urinary vanillylmandelic acid is now normal.

Case 11: Male. At birth, on May 14, 1956, he was noted to have extreme flaccidity of lower limbs and tumour was felt in right loin. At 3 weeks of age he was admitted here in satisfactory general condition. A large firm palpable mass obliterated right costolumbar angle. Radiographs of abdomen and spine revealed mass of calcification to right side of second and third lumbar vertebrae. Spinal canal appeared slightly widened and pedicles thinned with some suggestion of calcification within canal. There was some new bone formation along shaft of left femur. Biopsy of primitive neuroblastoma was performed by posterior retroperitoneal approach. Vitamin B12, 1 milligram intramuscular, every second day was given for three years as sole form of treatment. In March 1957 abdominal mass had become impalpable. There was still flaccid paraplegia of both legs, without sensation. Erosion of pedicles of vertebrae had disappeared and radiographs of long bones and skull were normal.

He is now alive aged 6 years and 7 months, without recurrence of abdominal tumor. There is no evidence of return of motor power to lower limbs, and he had ureteroileostomy for recurrent urinary infection. His vanillylmandelic acid test in June 1962 was normal.

Case 19: Female, born August 18, 1958. Enlarged abdomen noticed at 5 months, and at 7 months she was admitted to local hospital, and referred here at 8 months, where gross liver enlargement was found with slightly nodular firm surface. Right lobe extended to right iliac fossa. She was slightly wasted. Haemoglobin 69%; platelets 33,000/mm^3. Intravenous pyelogram (IVP) showed downward and medial displacement of right kidney but normal calyces. Laparotomy on April 29, 1959, at 8 months revealed that mass was enlarged liver with mottled appearance due to secondary deposits. A biopsy showed diffuse replacement of liver tissue by neuroblastoma with intervening fibrosis. Vitamin B12, 1 milligram, was instituted as sole form of therapy, and was given daily for first three months and on alternate days for remainder of three years. After four months some regression of liver was noticed, and this improvement continued progressively. One year after onset of treatment there was only slight liver enlargement and consistency felt fairly normal. After two and a half years liver was considered to be of normal size and consistency. At end of three years' course, and before ceasing treatment, IVP was normal, there being slight calcification in region of left adrenal. At second laparotomy liver was of normal size, containing firm areas of whitish tissue, suggesting some scar formation, but otherwise grossly normal. In left adrenal area walnut-sized lump was felt but not seen. Two biopsies were taken, one from normal-appearing area and other from a whitish area. Normal-appearing area was histologically normal, and whitish area showed some scar formation as well as Schwann cells and few quite mature ganglion cells, but no neuroblasts. Vanillylmandelic acid level was normal; vitamin B12 was discontinued. She is now well with no signs of recurrence of tumour, aged 4 years 4 months, about four years after symptomatic onset of disease.

Special Pattern of Widespread Neuroblastoma with a Favourable Prognosis

D'Angio GJ; Evans AE; Koop CE

Lancet : May 22 1971; 1046-1049

Extracted Summary

There is a group of children with disseminated neuroblastoma with a surprisingly good prognosis. Patients who fit the syndrome can have widespread disease in the liver, skin, and bone-marrow, or any combination of these. The primary tumour in some may be relatively small. Twenty-one of 25 such patients (84%) survived for two years or longer. Radiation therapy and chemotherapy may not be necessary in the management of certain children with this syndrome.

Selected Case Report

A five-month-old boy was well but was noted to have an abdominal mass on a routine "well-baby" examination in September 1962. He was alert and robust, and abnormal physical findings were limited to the abdomen. The grossly enlarged liver extended to a point 3 centimeters above the inguinal ligament. Chest x-ray normal; intravenous urography showed no displacement or distortion of the collecting systems; no calcification in the enlarged liver nor in the suprarenal regions. Bone marrow not aspirated. Total urinary vanillylmandelic acid content in a twenty-four hour sample was raised (40.7 milligrams, compared with normal twenty-four hour excretion for the age of 0.1-1.3 milligrams). At laparotomy, irregular nodules throughout the liver and a non-encapsulated tumour arising from the right adrenal extending through the diaphragm into the posterior mediastinum were found. The abdominal portion of the tumour was removed and a biopsy taken from the liver; histologically, both were neuroblastoma. No further treatment was administered. The boy grew and developed normally. The liver regressed in size and was not palpable one year after operation. Eighteen months after initial diagnosis liver biopsy showed normal hepatic tissue only. The vanillylmandelic acid level was normal. When last seen (1970) he was a normal, healthy eight-year-old boy with no evidence of disease.

Spontaneous Regression of an Untreated Neuroblastoma

Carvalho L

British Journal of Ophthalmology 57(11): Nov 1973; 832-835

Extracted Summary

The survival of patients with neuroblastoma (Vogel and others, 1970) is closely related to the natural history of the tumour. The age at onset of the disease, the site of origin of the lesion, the presence or absence of osseous metastases, and the spontaneous disappearance or maturation of the tumor are all of prognostic importance. Summaries of the literature are presented with discussions of different treatments.

The case presented in this paper is interesting in that spontaneous cure appears to have taken place in the presence of bony metastases with no therapy whatsoever.

Selected Case Report

A baby boy, born at full-term after a normal gestation on September 9, 1949, was admitted to hospital at the age of 4 months with a swelling on the outer side of the right eye. The cardiovascular and respiratory systems showed no abnormality. A large abdominal mass extended from the left costal region to the umbilicus, and numerous small lumps were palpable in the skin.

There was a smooth, fluctuant swelling at the right upper lid, right parietal region, and on the right ramus of the mandible, and small swellings on several ribs as well as in the subcutaneous tissue of the chest and left axilla. A biopsy of the left axillary gland on January 28, 1950, established the diagnosis of neuroblastoma (Dr. W. K. McGinley).

Because of the extent of the metastases, the child's poor general condition, his remote chances of survival, and the mother's reluctance for treatment to be undertaken, he was taken home. Much to the surprise of the Pediatric Unit, the mother returned with the child a year later. Most of the secondaries had disappeared and the primary swelling was considerably smaller, only one-third of its original size. It was then thought that this was one of the rare spontaneous cures, but a radiograph of the skull showed deposits of secondary tumours in the frontal, parietal, and sphenoidal bones. The abdominal mass was occupying the entire left upper quadrant. There was no readily available piece of tumour tissue for another biopsy. A full blood analysis was reported as normal. A radiograph dated February 1951, was described as follows:

Skull: Soft tissue swelling over the region of right orbit with some destructive bone changes. There is also possibly some bone thinning in the lesser wing of the sphenoid and also in the greater wing behind the eye. There is also an area of osteoporosis about the size of a half-penny in the mid-parietal region on the right side. The appearance is compatible with that of secondary metastases.

Abdomen: There appears to be a mass with calcification in the left renal area (Dr. G. Scarrow)

The patient was re-admitted to hospital on May 28, 1954, being now aged 3 1/2 years because of pain in the right eye and a discharge from both eyes. The abdominal mass was still palpable. The eyes showed right and left mucopurulent conjunctivitis and right scleritis. This cleared with local treatment and the patient was sent home.

Three years later the main complaint was swelling over the right eye and of the right upper eyelid and also that the eye was pushed forwards and downwards. The

abdominal mass was still palpable. Eye examination at the time showed the presence of an enlarged right lacrimal gland and displacement of the eye downwards and inwards. There was also diffuse soft swelling of the upper eyelid. The neuroblastoma was thought to be active by one pediatrician but not by the other. No treatment was given because of the mother's continued reluctance for her child to be subjected to surgery.

In October 1964, after a further 10 years, there was a large tumour involving the right upper lid extending back to the orbit. The right eye was displaced downwards. There were also what appeared to be a soft swelling of the right temporal fossa and behind the right ear, and this was thought to be due to the presence of secondaries. Plastic surgery, though considered at the time, was not carried out because of the underlying displacement of the right eye and destruction of the bony orbit.

Ocular examination in February, 1969, when the patient was aged 19 years, showed the visual acuity in the right eye with –1.5 D sph, + 3 D cyl, axis 105° to be 6/60. The visual acuity in the left eye without correction was 6/6. There was swelling of the right temporal region, the right upper lid was edematous and ptosed, and the fundi were normal. The pupils were equal and reactive to light, and the ocular movements showed limitation of elevation and abduction.

A skull radiograph taken in 1972, when the patient was 22 years old, was reported as follows: There is a deformity of the superior margin of the right orbit. There is some linear sclerosis of the occipital region on the right side. Similar sclerosis giving a bizarre appearance is present in the parietal region on the right side. I believe this patient has had neuroblastoma. The appearances are compatible with metastases in the skull vault and possibly in the right orbit.

Pelvic Neuroblastoma

A Better Prognosis

Ghazali S

Annals of Surgery 179(1): Jan 1974; 115-118

Extracted Summary

Seven children with pelvic neuroblastoma between the ages of 2 weeks and one year eleven months at the time of diagnosis are described. Six are alive, having undergone spontaneous maturation/regression; the seventh child died of intestinal obstruction but the pelvis was free of tumour. The better prognosis is considered to be due to the young age at the time of presentation and the site of the tumour.

Selected Case Reports

In November 1950, B. C., a male infant, 7 months of age, was admitted with acute retention of urine. Suprapubic cystostomy drainage revealed a large, fixed presacral mass which was encircling the rectum. Biopsy through the rectal wall showed the tumour to be undifferentiated neuroblastoma. Surgical excision was not contemplated due to the child's poor general condition. Radiotherapy was considered, but not given. Vitamin B12 was administered. At the age of 11 months the tumour could not be palpated per abdomen. Rectal examination showed some infiltration in the region of the prostate. Laparotomy at the age of 22 months revealed only two retroperitoneal nodules to the left of the sacrum. He is now 22 years of age and free of tumour.

A female child, C. C., born in August 1954, had sacral tumour noticed at birth. Biopsy of the tumour at the age of 3 months was first reported as chordoma. Histological examination at the Hospital for Sick Children, London, revealed this to be undifferentiated neuroblastoma. No treatment was given. At the age of 2 years and 3 months she had a large, mobile, soft mass palpable in front of the rectum and attached to its walls. Partial excision was performed leaving half the mass in situ. The specimen weighed 93 grams and consisted largely of mature ganglioneuroma but showed some residual areas of immature neuroblastoma. Vitamin B12 was given for 2 years. At the age of 8 years and 4 months a small nodule was palpable on the anterior surface of the sacrum, rectally, but at the age of 17 years she is free of tumour and of symptoms.

Spontaneous Regression of Disseminated Neuroblastoma

Schwartz AD; Dadash-Zadeh M; Lee H; Swaney JJ
Journal of Pediatrics 85(6): Dec 1974; 760-763

Extracted Summary

Two infants with disseminated neuroblastoma experienced spontaneous regression and recovery without the benefit of therapy. A review of present knowledge of this disease indicates that children under one year of age with a specific pattern of metastatic involvement may have a good chance of experiencing a spontaneous regression. The authors suggest that these infants be observed for a period of time before a decision is made to initiate therapy.

Selected Case Reports

Case 1: N.G., a one-week-old black girl, was referred to Children's Memorial Hospital because of hepatomegaly. Her liver was palpated to the level of the umbilicus. A liver-spleen scan demonstrated abnormal radionuclide localization in the right hepatic lobe. Biopsy of the liver yielded tissue diagnostic of neuroblastoma. Intravenous pyelogram, bone marrow examination, and roentgenographic examinations of the chest and skeleton were normal. Urinary excretion of vanillylmandelic acid (VMA) measured at 12 days of age was elevated to 240 micrograms/mg of creatinine (normal: 20 micrograms/mg creatinine or less). A diagnosis of neuroblastoma was made which involved the liver, although the location of the primary tumor was undetected. No therapy was administered, and the child was carefully followed as an outpatient. The liver slowly decreased to normal size over the ensuing months. On liver-spleen scans performed at 2 and 3 months of age there was only minimal localization of radionuclide in the right lobe. On a scan done at 9 months there was no evidence of localization. During this period of time the urinary VMA values decreased progressively to 147, 25, 21, and 10 micrograms/mg of creatinine at one, two, three, and five months, respectively. At one year of age the child is well with no clinical, roentgenographic, or chemical evidence of tumor.

Case 2: M. L., a two-month-old Caucasian girl, was referred to Children's Memorial Hospital with a chief complaint of "lumps in the skin" since birth. The lesions were purple and blanched with pressure. A biopsy of one of the skin lesions was diagnostic of neuroblastoma. Results of a bone marrow examination, liver-spleen scan, and roentgenograms of the chest and skeleton were normal. An intravenous pyelogram revealed lateral displacement of the left ureter suggesting a left paravertebral mass. Urinary VMA excretion was elevated to 90 micrograms/mg of creatinine. A diagnosis of disseminated neuroblastoma was made, the primary tumor probably arising from a left paravertebral sympathetic ganglion in the abdomen. No therapy was administered and the child was followed as an outpatient. The skin lesions completely resolved by 4 months of age, at which time a repeat intravenous pyelogram was normal with no evidence of a paravertebral mass. The urinary excretion of VMA decreased to 8 micrograms/mg creatinine. At 6 months of age the child appears well and has no evidence of neuroblastoma.

Spontaneous Regression of Neuroblastoma

Evans AE; Gerson J; Schnaufer L
National Cancer Institute Monographs 44: 1976; 49-54

Extracted Summary

Cases of spontaneous regression of neuroblastoma continue to occur in the present multimodal therapy era at institutions where physicians are prepared to withhold treatment on certain patients with residual primary or metastatic disease. From a survey of the 22 member institutions of Children's Cancer Study Group, seven hospitals submitted data on 24 neuroblastoma patients whose disease underwent regression after minimal, unusual, or no treatment. An analysis of these patients and of 33 patients from two large series in the literature shows that the majority of patients are infants with Stage II or Stage IVS disease. The spontaneous regression usually consists of complete disappearance of the disease, but in some neuroblastomas, maturation to ganglioneuroma takes place. The various factors that may influence regression are discussed.

Selected Case Reports

Case 1: A newborn girl was seen in 1970 at 3 days of age because of a large abdominal mass. Abdominal exploration showed the mass to be caused by a grossly enlarged liver infiltrated with tumor which proved to be neuroblastoma. No evidence of a primary neoplasm was found at that time. No treatment was given, and the liver gradually decreased in size over a period of 10 months. The baby was reexplored at the age of 1 year, and no evidence of tumor was found in the liver. A small mass was palpated in the left adrenal, which was removed and found to contain a small neuroblastoma. Again, no treatment was given, and the child remains well 3 years later.

Case 2: A 4-year-old male was referred for treatment in 1960, after a biopsy of a large abdominal mass showed ganglioneuroma. In addition, there was a lesion in the superior-posterior mediastinum. The mediastinal mass was completely resected, and it too was a ganglioneuroma. A regional lymph node contained ganglioneuroma. A bone marrow aspiration revealed tumor cells in clusters of 5-15 cells.

One month later the large retroperitoneal mass was incompletely resected and proved to be ganglioneuroma without evidence of neuroblastoma. Five years later a needle biopsy of the residual abdominal mass again showed ganglioneuroma. The patient has remained asymptomatic for 14 years. Although ganglioneuroma is a benign tumor of the sympathetic nervous system, its presence in a lymph node and the bone marrow suggests that it originated as a malignant neuroblastoma.

Spontaneous Regression of Stage IV Neuroblastoma

Eklöf O; Sandstedt B; Thönell S; Åhström L
Acta Paediatrica Scandinavica 72(3): 1983; 473-476

Extracted Summary

Neuroblastoma presenting with wide spread osseous metastases (stage IV) is generally considered incurable. However, rare cases of spontaneous regression and cure are on record. This report deals with such a case in which an infant received steroids as sole treatment for developing skeletal pain. Established metastases to the brain, scalp and skeleton disappeared. Today 4.5 years later the patient is free from symptoms and signs of tumour.

Selected Case Report

A boy, A. H., was born in India, where his biological mother died from unspecified cancer. The boy, who at that time was 8 months old, had half a year earlier been brought to Sweden for adoption. Previously essentially healthy, the boy was admitted to hospital at 10 months of age with fever and a palpable abdominal mass. An 11 x 7 x 6 centimeter large tumour, deriving from the right adrenal, was surgically removed. Neither local glandular or liver nor distant skeletal or pulmonary metastases were found.

Macroscopically the cut surface of the tumour was lobulated, grey-tan with areas of necrosis and hemorrhage. Microscopically the neoplasm consisted of sheets of nuclei and fibrillary material subdivided by fibromuscular septa. The nuclei were vesicular containing a very small nucleolus. A moderate amount of mitoses but no mature ganglion cells were seen. Calcification was present. The fibrous septa and the tumour tissue were moderately infiltrated by lymphocytes. The tumour was histologically interpreted as a differentiated neuroblastoma.

Considering the age of the boy and the seemingly radical extirpation no adjuvant treatment was applied. Recovery was uneventful but for a slight wound infection with culture proved growth of staphylococci.

Four weeks after discharge from hospital the patient was readmitted with fever and reduced mobility of the right arm. Roentgenograms of the humerus showed a suspect periosteal reaction but a scintigram was negative. Considering the unspecific manifestations and the previous wound infection, treatment with antibiotics was initiated resulting in abatement of the symptoms. However, relief was only temporary and the patient was soon readmitted having developed a right-sided exophthalmus, torticollis and multiple skeletal metastases, in addition to recurrent fever. At this point the condition was regarded incurable and the patient discharged with analgesics described for the increasing skeletal pain. However, the employed drugs proved inadequate pain relief and they were replaced by a daily dose of 15 milligrams prednisolone. In spite of continuing dissemination of osseous metastases and development of secondaries in the brain and scalp the pain diminished, finally disappearing completely. The boy's increasingly cushingoid appearance induced gradual withdrawal of the steroid, completed approximately 4 months after initiation of therapy and 10 months after the operation. During this period urine vanillylmandelic acid (VMA) and HVA values continuously increased then suddenly dropping to normal.

Beginning approximately at the time of steroid withdrawal gradual healing of the metastases ensued with normalisation or near normalisation of the skeletal structure. The patient's physical and mental development has been completely normal. Today 4 1/2 years after diagnosis of the tumour he lives in good health without any symptoms or signs of recurrence.

Complete Pathologic Maturation and Regression of Stage IVS Neuroblastoma Without Treatment

Haas D; Ablin AR; Miller C; Zoger S; Matthay KK
Cancer 62(4): Aug 15 1988; 818-825

Extracted Summary

Spontaneous maturation of Stage IVS neuroblastoma has been postulated as a mechanism for its favorable prognosis, but this has rarely been documented pathologically. We report on a patient with congenital Stage IVS neuroblastoma who had extensive subcutaneous and bone-marrow involvement. Serial photographs, biopsies, and vanillylmandelic acid determinations documented the tumor's initial progression which was followed by spontaneous maturation and involution of the patient's disease over a 6-year period. No cytotoxic therapy was administered. Favorable biologic prognostic factors were documented, including tumor DNA and protein analyses for N-myc amplification or overexpression and analysis for serum neuron-specific enolase and ferritin. Implications for management and therapy of Stage IVS neuroblastoma are discussed with reference to this case and the recent literature.

Selected Case Report

The patient was a 3.6 kilogram infant boy born in 1979 after a full-term pregnancy with normal labor and delivery. Though vigorous at birth, the infant was noticed to have many subcutaneous nodules and a palpable abdominal mass in the left upper quadrant. Examination of peripheral blood showed a leukocyte count (WBC) of 12,000 cells/microliter (neutrophils 61%, lymphocytes 34%, monocytes 5%) and a platelet count of 390,000 cells/microliter. Liver function tests were normal. Neoplastic cells were present in clumps of two to four in a bone-marrow aspirate. Computed tomography (CT) revealed a left calcified suprarenal mass 5 centimeters in diameter which did not cross the midline; a liver-spleen scan was negative. A bone scan showed multiple subcutaneous areas of uptake but no bony involvement. Biopsy of a subcutaneous nodule showed a malignant, densely cellular, poorly differentiated neoplasm composed of cells with large nuclei, ill-defined borders, and prominent mitotic activity consistent with neuroblastoma. The diagnosis of congential neuroblastoma (Stage IVS) was corroborated by a markedly elevated vanillylmandelic acid (VMA) of 240 micrograms/mg of creatinine (normal for age, <36).

The child was observed closely, but no surgery or chemotherapy was used. Though he continued to be vigorous and grew normally during subsequent weeks, an increase was noted in the size and number of the subcutaneous nodules. At six weeks of age, an intravenous pyelogram (IVP) showed an inferior displacement of the left kidney by the previously noted calcified left suprarenal mass, which was unchanged in size according to CT body scan. In addition, the scan revealed no hepatic nodules, and liver function continued to be normal. The patient's hemoglobin had decreased to 8.4 gm/dl while WBC and platelet count remained normal. The urinary VMA rose to 755 micrograms/mg of creatinine.

At age 3 months, the patient developed diarrhea, weight loss, right otitis media, and a skin rash. His subcutaneous nodules showed further progression. He was pale and irritable, with anasarca and hypoalbuminemia. Cultures of blood and the skin rash were positive for Staphylococcus aureus. He received a blood transfusion because of progressive anemia associated with tachycardia and tachypnea. Hemoglobin and hematocrit values were 4.2 gm/dl and 13.7%, respectively, although WBC (9200 cells/microliter) and platelet count (352,000 cells/microliter) remained normal. Because of diarrhea, positive occult blood in the stools, and hypoalbuminemia, serum vasoactive intestinal peptide was measured, but his value of 43 picograms/ml (normal, 38-110) ruled this out as a cause. The hypoalbuminemia and skin rash resolved after treatment with nafcillin. After the blood transfusion, hemoglobin stabilized at 10.2 gm/dl for 6 months; it finally normalized at 12.4 gm/dl by age 10 months. Subsequent complete blood counts remained normal. Liver function remained normal throughout the patient's course, except for one episode of serology-proven type A hepatitis.

An IVP done at 4 months of age revealed an incomplete ureteropelvic junction obstruction on the left, secondary to the tumor masses. The partial obstruction resolved within several weeks. Though the patient received no

chemotherapy, the multiple subcutaneous nodules increased to their maximal size at age 4 months and subsequently decreased in size. The VMA reached a maximum value of 2713 micrograms/mg of creatinine at 6 months; then gradually it decreased to normal. The status of the neuroblastoma was monitored with serial biopsies of remaining nodules at 4.5 months, 16 months, 36 months, and 76 months of age. The subcutaneous nodules at birth and at 4.5 months showed metastatic neuroblastoma involving soft tissue, but subsequent biopsy specimens showed ganglioneuroma consisting pricipally of mature ganglion cells and intervening Schwann cells without mitoses, and in some areas, only fibrotic scar was found. At age 3, examination revealed a persistant calcification and left suprarenal mass. The adrenal gland was removed but contained no viable tumor; it had central necrosis and calcification.

Analysis of the primary tumor at 36 months for N-myc gene amplification by Souther blot hybridization and for N-myc expression by immunostaining with antibody to the N-myc protein showed a single copy of the oncogene and no increased expression in the tumor. Serum neuron-specific enolase was 109.6 nanograms/dl, and ferritin was 105 nanograms/dl by radioimmunoassay. A bone scan at age 6 years, 9 months showed no abnormal areas. At present (age 8), there is no evidence of neuroblastoma by physical, radiologic, or VMA examination.

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