Endocrine late effects of childhood neuroblastoma therapy

The 20 years' experience of a single center

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INTRODUCTION

- **Neuroblastoma** is a childhood neoplasia affecting extracranial neuroectodermal tissue and accounting for about **10%** of solid childhood malignancies, which represents 1/100.000 children every year
- Survival rate approach 70%, leading to the emergence of a population of adult survivors having been exposed to adverse effects of cytotoxic drugs or therapy.
- Adequate management of **late effects** require appropriate awareness and knowledge of them.
- Patients treated for neuroblastoma are exposed to **surgery**, **chemotherapy**, **radiotherapy** or **MIBG** therapy. All those treatments potentially affect the endocrine and gonadal system.

AIM

Our work consists in a **retrospective** review of **endocrine and gonadal late effects** arising in survivors treated for neuroblastoma in childhood.

MATERIAL & METHODS

- We **retrospectively** reviewed medical files of **50** patients (M/F = 27:23) treated for neuroblastoma between 1994 and 2016.
- **Collected data** consisted in age, height, and weight at diagnosis as well as age, height, and weight at the time of last endocrine follow-up. Standard deviation values were computed for those parameters to enable comparison. Biological value such as TSH, T4, FSH, LH, ACTH, IGF-1 were recorded at the time of last follow-up.
- Incidence of late effect in our sample was **compared** to incidence of late effects due to neuroblastoma therapy in larger series.
- Statistical analysis through ANOVA with repeated measures (STATISTICA Software) were conducted to study impact of chemotherapy on height and weight at follow-up

RESULTS

Variable	N	Mean	Ecart-type
Age at diagnosis (months)	50	27.3 (0-190)	36.41696
Height at diagnosis (cm)	31	95.2 (49-156)	29.79288
Height at diagnosis SD	31	0.29 (-4.7-4.8)	1.76332
Weight at diagnosis (kg)	35	15.6 (3,095-42)	10.54788
Weight at diagnosis SD	34	-0.007 (-4,1-4,9)	1.50334
BMI at diagnosis	20	16.3 (11.9-21,4)	2.73801
BMI at diagnosis SD	20	-0.44 (-5-1.9)	2.00027
Age at follow-up (years)	27	11.7 (1-25)	6.83161
Height at last follow-up (cm)	28	138.12 (77-181.4)	32.84159
Height at last follow-up SD	27	-0.35 (-4-2)	1.34503
BMI at last follow-up	24	19.23 (13.5-34.7)	5.17372
BMI at last follow-up SD	23	-0.25 (-1.6-2.7)	1.26415
Weight at last follow-up (kg)	27	39.4 (9.33-90)	24.31822
Weight at last follow-up SD	26	-0.16 (-2.7-2.2)	1.25885
Growth rate (cm/year)	14	4.68 (0.9 - 9.9)	2.46707
Growth rate SD	10	-0.09 (-1.3-0.9)	0.75048

- **Age** : Patients included in study were between 0 and 190 months old at diagnosis (mean: 27 months) and between 1 and 25 years-old at follow-up (mean: 11.6 years).
- **Treatment** : **26** patients were treated with **chemotherapy**, **11** underwent **radiation therapy** and **5** were treated with **MIBG** therapy. Others were treated with **surgery alone**.
- **Prognosis and sequelae**
  - 5 deceased (10%, 12% in chemotherapy group)
  - 4 gonadal dysfunction (male, female) (8%, 16% in chemotherapy group)
  - 7 hypothyroidism (14% , 20% in chemotherapy, 100% in MIBG)
  - Non-endocrine complications
    - Partial deafness (n=4), neuropathy (n=1),
    - hypogammaglobulinemia (n=3)
    - alopecia (n=2), osteopenia (n=1)
- **44%** of **endocrine complications** in **chemotherapy** group, **18%** in patients treated with **chemotherapy and radiation therapy**

RESULTS

- There is **no effect** of chemotherapy on **weight** at follow up
- There is a **significant impact** of chemotherapy on **height** after treatment ($p<.05$, mean of height standard deviation at diagnosis = . 0.9 and at follow up = -.59).
- The effect of chemotherapy on patients' **growth rate depended on age at diagnosis** ($p=.016$) (Regression analysis), which means that the younger the treatment was started, the more severely growth was impacted.

DISCUSSION

- Neuroblastoma are divided as either low or high risk, depending on age at diagnosis, localization, cytogenetic factors and presence of metastasis. Low-risk neuroblastoma mainly occur in children below 12 months of age and are often managed with surgery only. If localization of tumor makes it inoperable, chemotherapy is used as first line of therapy. High-risk neuroblastoma therapy require chemotherapy, MIBG therapy, radiation therapy, and sometimes autologous hemotopoietic stem cell transplant
- In large follow-up series, **late effects** of neuroblastoma therapy affect **89%** of patients, and endocrine complications affect **62%** of female and **45%** of males treated for childhood neoplasia*.
  - Deafness (55-73%)
  - Ovarian failure (38%, 75% for females >13 years-old)
  - Hypothyroidism (23%)
  - Neurological complications (11%)
  - Scoliosis (15%)
  - Pulmonary complications (11%)

TOXICITY BY THERAPEUTICAL AGENTS

Alkylating agents (carboplatine, cyclophosphamide):
- **Ovarian failure**
- **Testicular dysfunction**
- Dental abnomalies
- Lung fibrosis
- Renal impairment and tubulopathies
- Second malignancies (MDS/leukemia, thyroid)

Radiation therapy
- **Ovarian failure**
- **Leydig cell failure**
- **Growth deficiency and impaired growth (scoliosis)**
- Severe dental abnomalies
- Second malignancies (MDS/leukemia, thyroid)

MIBG therapy
- **Hypothyroidism (50-80%)**
- Second malignancies

Surgery
- Neurological complications

Ovarian failure
- Prepubertal state during therapy protect against ovarian failure, which is not always definitive

Growth impact
- Final height is affected in children not treated with TBI, and without biological GH deficiency **

CONCLUSION

- Treatment for childhood malignancies exposes children to late effects affecting, among other, the endocrine system. In children treated for neuroblastoma, **hypothyroidism, gonadal failure and altered growth** appear as the main complications. A close follow-up of survivors is thus highly appropriate.

* Laverdière C, Liu Q, Yasui Y, et al. Long-term Outcomes in Survivors of Neuroblastoma: A Report From the Childhood Cancer Survivor Study. J Natl Cancer Inst 2009;101:1131-1140
**Cohen LE, Gordon JH, Popovsky EY, et al. Late effects in children treated with intensive multimodal therapy fo high-risk neuroblastoma : High incidence of endocrine and growth problems. BMT. 2014;49:502-508.

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