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Childhood medulloblastoma

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Contents

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ABSTRACT

Medulloblastoma accounts for 15–20% of childhood nervous system tumours. The risk of dying was reduced by 30% in the last twenty years. Patients are divided in risk strata according to post-surgical disease, dissemination, histology and some molecular features such as WNT subgroup and MYC status.

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Sixty to 70% of patients older than 3 years are assigned to the average-risk group. High-risk patients include those with disseminated and/or residual disease, large cell and/or anaplastic histotypes, MYC genes amplification. Current and currently planned clinical trials will:
(1) evaluate the feasibility of reducing both the dose of craniospinal irradiation and the volume of the posterior fossa radiotherapy (RT) for those patients at low biologic risk, commonly identified as those having a medulloblastoma of the WNT subgroup;
(2) determine whether intensification of chemotherapy (CT) or irradiation can improve outcome in patients with high-risk disease;
(3) find target therapies allowing tailored therapies especially for relapsing patients and those with higher biological risk.

1. General information

1.1. Incidence

Among all the childhood central nervous system (CNS) tumours, medulloblastoma and other neuroectodermal tumours (International Classification of Disease for Oncology – ICD-O codes 9470/3–9474/3) account for 25% of all CNS tumour cases in children (RARECAREnet, 2016), 15–20% represented by medulloblastoma. The European annual incidence rate was 6.8 per million children (age: 0–14 years) for the period 2000–2007, with high rates in Southern and Central Europe (RARECAREnet, 2016). Incidence was significantly higher in boys than in girls (about 40%). The annual incidence rate was higher in children between 1 and 9 years of age, slightly less than 8 per million; it was lower in infants (6 per million), and the lowest in 10–14-age children (4 per million) (Peris-Bonet et al., 2006). The incidence rate is higher in the age group 15–19 years (2.33/million/year) and decreases up to age 40, consistent with the embryonal origin of the tumour (Giordana et al., 1999). Rising incidence was recorded for medulloblastoma during the period 1978–1997, by 1.3% on average (Peris-Bonet et al., 2006). Incidence in North-America has been reported as 5.07 per million children (age: 0–19 years) (Kohler et al., 2011). For comparison, at the Children's Cancer Hospital Egypt between 2007 and 2013, on a total of 1114 diagnosis of brain tumours, embryonal tumours represented the 23.2% of the total, thus showing consistency with Europe and North America (Ezzat et al., 2016).

1.2. Survival

In European children with a medulloblastoma diagnosed in the period 2000–2007, 1-, 3- and 5 years survival figures were 81%, 63% and 56%. Infants had a worse prognosis: 5-year survival was 33%, slightly better for children aged 1–4 years (47%), while prognosis was significantly better (67%) for the age group 5–14 years (Kohler et al., 2011). Survival remained stable during the period 1999–2007 (Gatta et al., 2014), while it improved during the end of Nineties: the risk of dying reduced significantly by 30% (Gatta et al., 2009). Standard of care treatment for children older than 3–5 years entails surgical resection, craniospinal irradiation, and CT that has resulted in an overall cure rate, in clinical setting, of approximately 70–75% (Gatta et al., 2014; Gatta et al., 2009; Lannering et al., 2012). Outcome varied across European countries, suggesting difficulty to access to effective treatment and/or to reach timely and correct diagnosis. Actually, 5-year survival was better in Northern Europe (64%) and lowest in Eastern (53%) European countries (Gatta et al., 2014).

1.3. Risk factors

The peak of incidence of medulloblastoma/PNET (MB/PNET) occurs during childhood; therefore, factors operating very early in life might play a key role. Birth weight has often been suggested to be a rough but easy indicator of prenatal exposures. Harder et al. conducted a systematic review on the association between birth weight and risk of specific histologic types of primary brain tumours. For medulloblastoma, high birth weight was significantly associated with increased risk (odds ratio—OR: 1.27; 95% CI 1.02–1.60) (Harder et al., 2008). Several studies have speculated on a potential infectious aetiology. A case-control study in England evaluated various perinatal factors and their impact on childhood brain tumour. The Authors found that the children of mothers who had a documented viral infection during pregnancy had 11-fold increased risk of malignant nervous system tumour (Fear et al., 2001). A further large population-based case control study investigated the patterns of day care and social contacts in the first year of life, as well as other markers of infectious exposure. Children reported to have had no social contact with other infants in the first year of life displayed an increased risk of developing a medulloblastoma (OR: 1.78; 95%CI 1.12–2.83) (Harding et al., 2009). However, other proxy markers of infectious exposure that were analysed (i.e., bedroom sharing, domestic exposure to school-age children, and birth order) did not support the hypothesis of a protective effect of infectious exposure. The role of diet, both as a risk and as a protective factor, has been investigated in several studies. Among the most extensively studied hypotheses is that maternal dietary intake of N-nitroso compounds (NOC) and NOC precursors during pregnancy increases brain tumour risk in offspring (Dietrich et al., 2005). Cured meats are a major source of dietary NOC. Maternal dietary was investigated in a large international collaborative case-control study on childhood brain tumours to evaluate associations between histology-specific risk and consumption of specific food groups during pregnancy. Foods generally associated with increased risk were cured meats, eggs/dairy, and oil products; foods generally associated with decreased risk were yellow-orange vegetables, fresh fish, and grains. However, cured meat was not associated with medulloblastoma. An increased risk was found between medulloblastoma and oil products (OR: 1.5; 95%CI 1.0-2.2 for 4th *vs.* 1st quartile; p trend = 0.005) (Pogoda et al., 2009). A large Canadian study (Li et al., 2009) examined the contribution of maternal occupational exposure to extremely low frequency magnetic fields (ELF-MF) shortly before and during pregnancy on the incidence of childhood brain tumours. A significantly increased risk was observed for astroglial tumours as well as for all childhood brain tumours, but no association was specifically assessed for MB/PNET (MB/PNET. Several epidemiological investigations have attempted to evaluate the association between parental exposure to pesticide and childhood brain tumours, with the majority reporting positive associations (Baldwin and Preston-Martin, 2004). In a population-based case-control study, the association between the occurrence of brain cancer in children and parental exposure to pesticides in occupational and residential settings was evaluated. The authors observed little association with PNET for any of