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BASIC CLINICO-PATHOLOGICAL FEATURES OF CONGENITAL TUMOURS*

OSNOVNE KLINIČKO-PATOLOŠKE KARAKTERISTIKE KONGENITALNIH TUMORA

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Apstrakt

Kongenitalni ili perinatalni (fetalni i neonatalni) tumori značajno se razlikuju od tumora kod adolescenata i odraslih po histološkim tipovima, incidenciji, biološkom ponašanju, kliničkoj prezentaciji i reakciji na terapiju. Još uvek nije potpuno jasno da li su izvesne tkivne izrasline pravi tumori, kongenitalne malformacije ili hamartomi. Histološki benigni tumori u novorođenčadi mogu da prouzrokuju smrt zbog svoje lokalizacije. Neki od kongenitalnih malignih tumora imaju dobru prognozu, a neki čak mogu da regrediraju ili se diferenciraju u benigne tumore. Kongenitalni tumori prezentuju se specifičnim znacima i simptomima kao što su polihidramnion, fetalni hidrops i distocija. Nastanak kongenitalnih tumora povezan je sa hromozomskim i genetskim promenama, a neki su povezani sa određenim sindormima i malformacijama. Histološka građa kongenitalnih tumora, kao i kliničke, epidemiološke i eksperimentalne studije dokazuju povezanost između embriogeneze, teratogeneze i kancerogeneze. Incidencija kongenitalnih tumora procenjuje se na oko 10 na 100.000 novorođenih. Vaskularne lezije se klasifikuju u vaskularne malformacije i tumore. Infantilini hemangiom predstavlja najčešću tumorsku leziju u uzrastu odojčeta. Najčešći kongenitalni tumori su teratomi (oko 25%), a sličnu učestalost imaju i neuroblastimi kao najčešći maligni kongenitalni tumori. Na listi učestalosti slede mezenhimski tumori (10%), tumori bubrega, mozga, histiocitoze Langerhansovih ćelija, hepatoblastomi i retinoblastomi. Relativna učestalost leukemija varira prema različitim studijama od 6-16%. Zbog retkosti i specifične kliničko-patološke prezentacije iskustva sa kongenitalnim tumorima imaju samo patolozi i klinički lekari u velikim porodilištima i dečjim klinikama.

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INTRODUCTION

The term congenital tumours comprises all tumour mass noted during pregnancy in utero by ultrasonography and after birth, during the first month of life. The term perinatal tumours is also commonly used. However, it is reasonable to suppose that any tumour presented in the first three months of life is congenital. Actually, the distinction between a congenital and an acquired tumour identified in the first year of life is difficult (1;2).

Congenital tumours are different from tumours in the older children, adolescents or adults in many features, such as the types, incidence, clinical presentation, behaviour, and response to treatment (1;2).

Classical histological criteria of malignancy are not always helpful or valid in the young. Rapidly proliferating normal embryonic cells may have some features of neoplastic cells. Thus, it is sometimes difficult to determine whether the analyzed cells or tissue belong to normally differentiating structures or a neoplastic process.

Not so rarely, it is difficult to distinguish between certain tumours, congenital malformations and hamartomas, as in case of vascular malformation and haemangioma, the most common congenital tumour mass in childhood (2;3). As a consequence of this dilemma several confusing terms for some entities coexist. Good example is a congenital nasopharyngeal “hairy polyp”, which was named as teratoma, dermoid, hamartoma or choristoma by different authors. According to the current concept this lesion is defined as choristomatous teratoid (hairy) polyp (4).

A cancer of identical histology may have a distinctly different prognosis in a newborn as compared to an older child or adult. The examples are fibrosarcoma, neuroblastoma and acute lymphoblastic leukaemia as noted in the text below. Histologically benign tumours and tumour-like conditions in the young may cause death because of their location (lymphatic malformation, fibromatosis, mature teratoma involving vital structures in the neck, mediastinum, or brain). Conversely, malignant tumours, as neuroblastoma cells may differentiate postnatally into mature ganglion cells or regress (2).

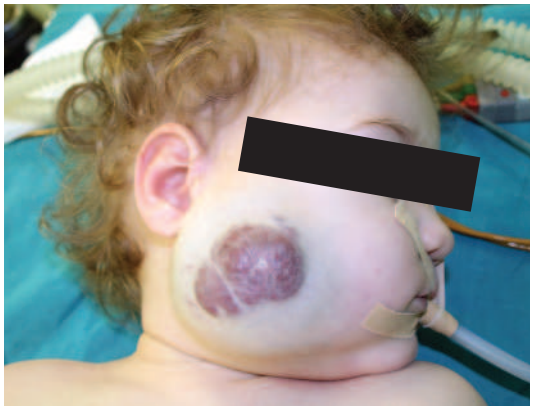

Figure 1. Twenty-month-old girl just before the operation of the infantile haemangioma noticed for the first time in the second week of life.

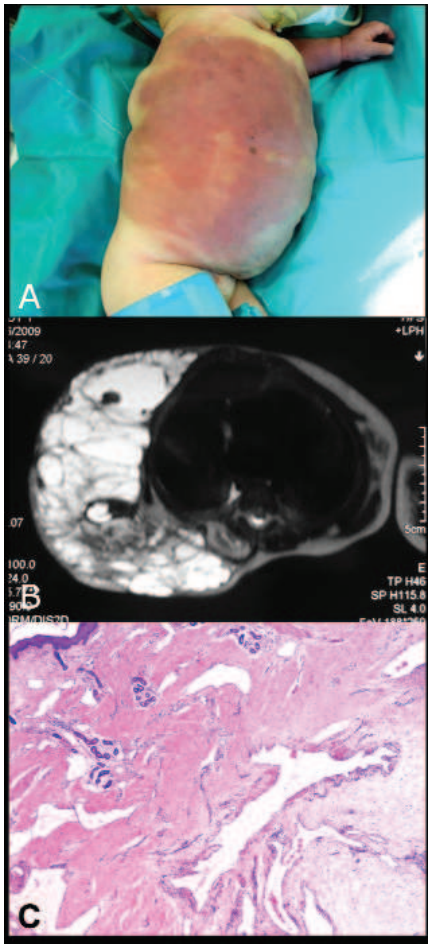

Figure 2. Combined capillary-venous malformation is diagnosed in utero by ultrasonography and, after unsuccessful attempt of sclerotherapy, partially resected in the nineth month of life of this male infant. A. Port wine stains-like lesion in the region of the huge congenital tumour-like mass. B. Magnetic resonance image reveals chest deformity caused by the huge multicystic mass involving the right side of the trunc. C. Histologic feature of ectatic capillary vesseles within the dermis and much larger, irregularly contoured lymphatic vesseles deeper in subcutanous tissue (HE stain, X50).

Perinatal tumours have some specific presenting signs and symptoms: polyhydramnios (due to difficulties in the fetal swallowing mechanism), fetal hydrops (circulatory obstruction or leaky tumour vessels in teratomas or vascular lesions, and cardiac dysfunction associated with rhabdomyoma), dystocia (space-occupying tumours), fatal exsanguination due to rupture of a large tumour (sacrococcygeal teratoma, neuroblastoma, hepatoblastoma) (2;5).

The 5-year survival rate of children with neonatal tumours was approximately 25% (2;6). This rate in the large Danish Cancer Registry study from 1992. was the highest in neonates with soft tissue sarcoma (55%), followed by those with neuroblastoma (25%), but all patients with leukaemia and brain tumours died (6).

AETIOLOGY

Genetic, chromosomal, syndromic and environmental associations have been recognized in congenital and childhood cancers.

Histological findings in congenital tumours are suggestive of an origin linked to abnormal embryogenesis and some neoplasms of childhood are collectively referred to as blastoma or embryonic tumours: neuroblastoma, nephroblastoma (Wilms' tumour), retinoblastoma, hepatoblastoma, medulloblastoma and embryonal rhabdomyosarcoma. According to Willis, who considered embryonic tumours to be both a neoplasm and a malformation occuring at the same time (7), embryonic tumours are not acquired lesions developing from a previously normally formed or malformed organ, but instead took their origine from some stage of development of that organ. Persistent embryonal or fetal tissue in congenital tumours suggests a failure of proper cytodifferentiation or maturation during early life (1;2;7;8). Relationship between embryogenesis and cancerogenesis is demonstrated by occurance of some embryonal tumours in heterotopic tissue, not rarely associated with other congenital malformations. One such example is the case of haemangioendothelioma arising in heterotopic hepatic tissue in the thoracic cavity of patient born with congenital diaphragmatic hernia (9-11).

An important relationship exists between inherited syndromes and congenital malformations and the development of neoplasms (2). Hereditary tumours only account for 2-4% of childhood cancers. The commonest are neurofibromatosis, 40% of retinoblastomas and 1-2% of Wilms' tumours (1;12;13). Many inherited syndromes predispose to tumour development. Some karyotypic abnormalities are specific to particular tumour types. One such example is the increased incidence of gonadoblastoma and germinoma in gonads of patients having XY gonadal dysgenesis.

Retinoblastoma and Wilms' tumour are sometimes associated with alterations of 13q ad 11p, respectively. In these locations Rb and WT genes were mapped. Tumorgenesis occurs only when both of alleles of these tumour supresor genes are altered. Transformation of proto-oncogenes into oncogenes by chromosomal translocation, point mution or gene amplification is the other genetic mechanism. One example is amplification of N-myc oncogene that is associated with an avanced stage and unfavourable outcome of patients with neuroblastoma (13-16).

Several sporadic dysmorphic syndromes and malformations carry significant risk of childhood cancer. Ten to 21% of children with Beckwith-Wiedemann syndrome develop neoplasms. Occasional occurrence of neuroblastoma in children with Hirschsprung's disease suggests that it may sometimes be part of a generalized disorder of neural crest development (1).

The association of non-syndromic malformations and childhood tumours was incompletely clear. In a review of the records of 20304 children with cancer in Great Britain, the frequency of anomalies were 4.4% in children with solid tumours, and 2.6% in those with leukaemia or lymphoma. The cancers most frequently associated with malformations were Wilms' tumour (8.1%), hepatoblastoma (6.4%), gonadal and germ cell tumours (6.4%) and Ewing's sarcoma (5.8%) (17).

There is good experimental evidence that teratogenesis and oncogenesis are closely linked, but, to date, there is no definite causal relationship has been established between environmental factors and congenital tumours (1;2).

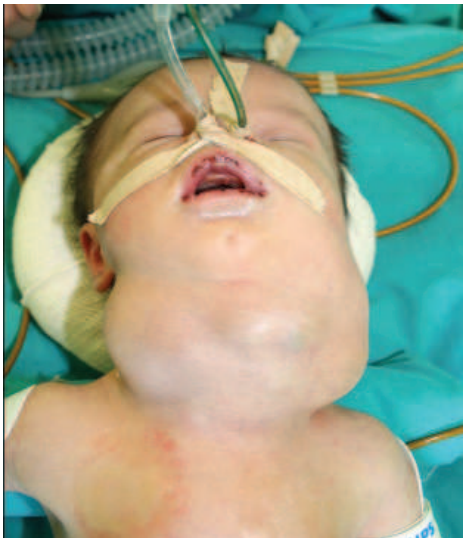

Figure 3. Congenital multinodular neck mass, after resection in first week of life histologically defined as the immature teratoma.

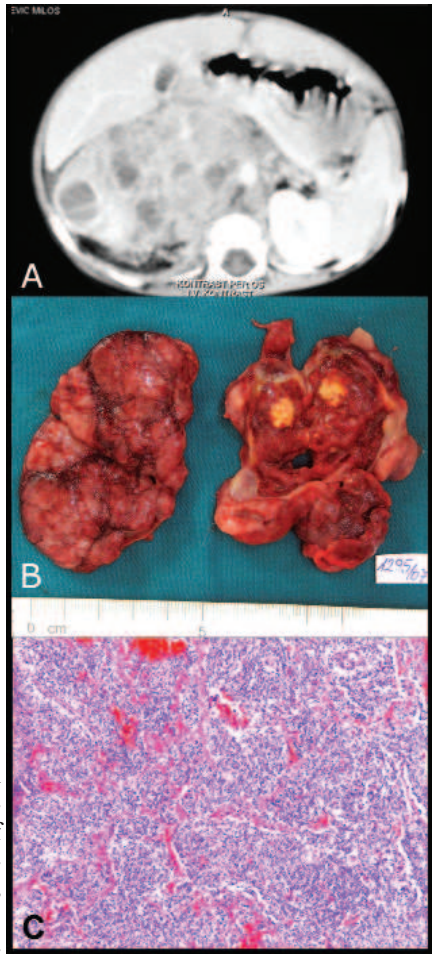

Figure 4. A large congenital neuroblastoma of the right adrenal gland. A. CT image with contrast emphasizes a lobular feature and heterogeneity of the tumour. B. Macroscopic feature of the lobular, encephaloid tumour mass. C. Microscopic finding of the small round cell tumour with nested pattern as one of the histologic features of poorly differentiated neuroblastoma (HE stain, X120).

INCIDENCE

Estimates of the incidence of congenital tumours are imprecise (2;18). Most published articles represent the experiance of individual health care centers where selection bias seems to reflect referral patterns (19). Benign perinatal tumours are common, but many may be unrecognized or unreported (1;2). Haemangiomas are present in 6-25% of the paediatric population, and about 20% are congenital. Melanocytic naevi are found in 1-3% of newborn white infants (1).

The Third US National Cancer Survey (1969-1971) estimated the incidence of malignant neoplasms in neonates as 3.65 per 100000 live births. Mortality rate was approximately one-fifth of that incidence, reflecting the relatively benign course of several histologically malignant tumours in this age group (20). A 30-year population-based study from the Children's Hospital of Birmingham, UK, revealed that the incidence of neonatal tumours is 7.2 per 100000 live births (18). Teratoma is the most common neoplasm identified in several perinatal studies and in a very small percentage of cases it is found to have malignant component. Almost the same incidence of approximately 25% of all perinatal tumours had neuroblastoma, the most common malignant congenital tumour, and it was followed by mesenchymal tumours of various types (10%), renal and brain tumours, Langerhans' cell histiocytosis, hepatoblastoma and retinoblastoma. Reported incidence of leukaemia was varied in different studies (6-16%) (2;18;21). A study of 17417 perinatal autopsies carried out in Melbourne, Australia, over five decades revealed 46 congential tumours (0.26%) including 24 teratomas, followed by vascular tumours, neuroblastoma, cardiac rhabdomyoma and mesoblastic nephroma in frequency (5).

SOME CHARACTERISTICS OF THE MOST COMMON CONGENITAL TUMOURS

Vascular birthmarks can be classified into vascular malformations and tumours. Infantile haemangioma are the most common tumours of infancy (4-12% of all white population) with a unique lifecycle: rapid growth in infancy, followed by a period of involution, leading to complete regression (Figure 1). Some of them must be treated (22;23). Immunohistochemical studies revealed that GLUT-1 stains 100% of infantile haemangiomas and none of the other vascular tumors and malformations. Congenital haemangiomas are fully grown in utero and they do not experience postnatal proliferation. Some of them (RICH - Rapidly Involuting Congenital Haemangioma) undergo spontaneous involution during the first year. Others (NICH - Non Involuting Congenital Haemangioma) persist life long (22;24).

Vascular (capillary, venous, arterial, lymphatic, and combined) malformations show a normal endothelial turnover, being persistent at birth and growing commensurately with the child. The sclerotherapy is possible intrauterine management option for lymphatic malformation (25;26) (Figure 2).

Most congenital teratomas are extragonadal. Sacrococcygeal teratomas outnumber all others (45%), followed by ovarian (30%), mediastinal (7%), testicular (3%) in frequency. Cervical teratoma account for 3-5% of childhood teratoma and show benign clinical behavior, but 17% of affected fetuses are stillborn and 35% die before surgery, generally due to airway and pulmonary compromise (Figure 3). Severe airway obstruction at delivery can be better managed by multidisciplinary perinatal care team able to provide ex utero intrapartum treatment (EXIT). Teratomas arise either from totipotent somatic cells or premeiotic germ cells and some are clonal. They are biologically different from teratomas in older children and adults (1;21;27-30). Immature, mostly neural element are common and are not an indicator of malignancy in neonates (1), but is associated with an increased risk of local recurrence (31). Overall, one in 40 congenital teratomas is malignant with a yolk sac tumour as an almost exclusive malignant component. Yolk sac tumour may occasionally be in small foci of mature or immature teratoma and hard to recognize (1;32), but surgical resection alone may be adequate therapy for those tumours (27). In the nonteratoma group, patients with pure yolk sac tumour and gonadoblastoma have a much better outcome than those with choriocarcinoma (27).

The primary site of congenital neuroblastoma is most commonly adrenal gland and retroperitoneum (Figure 4). The histology does not differ fom that in older children, but its behavior and metastatic pattern are distinctive (1). As a result of necrobiosis or maturation to ganglioneuroma, congenital neuroblastoma undergoes spontaneous regression more commonly than any other tumours (33). Relatively

benign behavior of neuroblastoma in neonates is the consequence of the fact that at least 30% of patient have a special pattern of metastases termed Stage IV-S (small primary tumours with dissemination to liver, skin and bone marrow, but without bone lesions) which has a particularly favourable outlook. Most of IV-S neuroblastoma lack the genetic mechanisms for fully malignant behavior, the most important being N-myc amplification (34;35).

Congenital mesenchymal tumours are usually benign. The fibrous proliferations - fibromatoses - are the most common and include a number of distinctive, locally invasive lesions. Fibromatoses in infancy are generaly more cellular than adult types, although the latter also occur in childhood. Infantile fibromatosis, myofibromatosis, haemangiopericytoma and congenital fibrosarcoma are usually regarded as separate entities, but it is newly recognized that there is considerable histological overlap, and that an individual lesion may show fetaures of more than one entity (1;36;37). Congenital myofibromatosis in its solitar form is the most common in the haed, neck and trunk, but multicentric form also involves skin and bone. Infantile desmoid-type fibromatosis, fibromatosis colli, infantile digital fibromatosis, juvenile hyaline fibromatosis, fibrous hamartom of infancy, cranial fasciitis and giant cell fibroblastoma may occur in neonatal period (1). Malignant soft tissue tumours are equally devided in frequency between congenital fibrosarcoma, rhabdomyosarcoma and other non-rhabdomyosarcomatous malignant soft tissue tumours (38). Congenital (infantile) fibrosarcoma is a different entity from adult-type fibrosarcoma with a better prognosis (metastases in <10% of cases and 84% 5-year survival rate). It characteristically showes trisomy of chromosome 11 and a specific t(12;15) in some cases (1;3). Rare cases of neonatal rhabdomyosarcoma are mostly rised in buttock, sacrococcygeal, perirectal and urogenital region and most of them are of embryonal type. Suprisingly, the patological finding revealed an alveolar type of rhabdomyosarcoma in our patient with large congenital orbital tumour (39). Plexiform neurofibromas are usually congenital and are almost pathognomonic of neurofibromatosis type I. Lipoblastoma and lipoblastomatosis are adipose tumours occasionally present at birth (1).

Between 5-7% of perinatal tumours arise in the kidney. Mesoblastic nephroma is the commonest. It is unrelated to Wilms' tumour which is found extremely rarely in this age. An intrarenal tumour mass resembling uterine leiomyoma enlarges the kidney. Histology shows spindle cell myofibroblast infiltrating normal kidney at its margins. The cellular variant of mesoblastic nephroma may be aneuploid and shows trisomy 11 and t(12;15) suggesting a histogenetic relationship to infantile fibrosarcoma (1;3;40). Rhabdoid tumour of kidney and extrarenal rhabdoid tumour share the same genetic change as 22q11 and are usually present in the first few months of life (1;3;40).

The important primary liver tumours of neonates represent infantile haemangioendothelioma, hepatoblastoma and mesenchymal hamartoma (1). Congenital leukaemia is rare. It differs from leukaemia in older children by much worse prognosis and in that about 50% are myeloid, and 25-30% of patients have skin involvement. Leukaemia is associated with Down's and several other syndromas (1;41). Langerhans' cell histiocytosis, haemophagocytic lymphohistiocytosis and juvenile xanthogranuloma represent group of histiocytic disorders that are commonly present in the neonatal period (42). Only 1% of childohood brain and spinal cord tumours occur in the neonatal period. They are mainly supratentorial and characterized by an enlargement of the head because of hydrcephalus or the mass by itself. The commonest are teratoma in the pineal region or in continuity with a pharyngeal teratoma (1).

CONCLUSION

Perinatal tumours arise from neoplastic change in immature embryonic or fetal tissue, or persistent stem cells and recapitulate the embryonic tissues in which they arise. Because of their rarity and specificity of clinico-pathological presentation only pathologist working in obstetric or neonatal/paediatric clinic or unit can expect to see occasional cases. Lack of familiarity with perinatal tumours may lead to unnecessarily aggressive therapy or well-intentioned neglect.

Abstract

Congenital or perinatal (fetal and neonatal) tumours are different from tumours in the adolescents and adults in histological types, incidence, biology, clinical features, prognosis, and response to treatment. Occasionally, it is difficult to distinguish between certain tumours, congenital malformations and hamartomas. Histologically benign congenital tumours may cause death because of their anatomic location. Conversely, most of malignant tumours have favourable prognosis and some of them may regress or differentiate postnatally into mature types. Classical histological criteria of malignancy are not always helpful or valid in the young. Perinatal tumours have some specific presenting signs and symptoms: polyhydramnios, fetal hydrops, dystocia. There is association between genetic and chromosomal alterations, congenital malformations, some syndromes and congenital tumours. Histological characteristics of congenital tumours, clinical, epidemiological and experimental studies confirm the close link between altered embryogenesis, teratogenesis and cancerogenesis. The incidence of perinatal tumours is around 10 per 100.000 live births. Vascular birthmarks can be classified into vascular malformations and tumours, infantile haemangioma being the most common tumour of infancy. Teratoma is the most common perinatal tumour. Neuroblastoma - the most common malignant tumour in that age, has almost the same incidence of 25%. They are followed by mesenchymal tumours (10%), renal and brain tumours, Langerhans' cell histiocytosis, hepatoblastoma, and retinoblastoma. Incidence of leukaemia has varied in different studies (6-16%). Because of their rarity and specificity of clinico-pathological presentation of perinatal tumours only pathologist and clinicians working in obstetric or neonatal/paediatric clinics can expect to see occasional cases.

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