Familial hemophagocytic lymphohistiocytosis: from autopsy to prenatal diagnosis. Report of a case

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SUMMARY

Hemophagocytic lymphohistiocytosis is a rare immunologic disorder affecting small children. It is characterized by an excessive and injurious immune response which turns rapidly fatal unless promptly and effectively treated. The main clinical signs are prolonged fever, hepatosplenomegaly, bleeding and laboratory findings of pancytopenia, increased serum transaminases, hypertriglyceridemia and hypofibrinogenemia. Four genes responsible for familiar hemophagocytic lymphohistiocytosis, which is inherited in autosomal recessive manner, have been identified so far. This case report describes a fatal case of familiar hemophagocytic lymphohistiocytosis caused by compound heterozygote mutation for perforin. A previously healthy neonate, first child of noncosanguineous young healthy parents, presented with hypothermia and fulminant hepatic failure at 28 days of life and succumbed short after. The diagnosis was made at autopsy and confirmed by genetic testing postmortem. Five months later prenatal testing confirmed carrier status in the sibling to be born. This is to our knowledge only the second case of familiar hemophagocytic lymphohistiocytosis caused by perforin deficit in a Czech patient.

Keywords: familial hemophagocytic lymphohistiocytosis – liver failure – hypothermia – neonate – prenatal diagnosis

Familiární hemofagocytující lymfohistiocytóza: od autopsie k prenatální diagnóze. Kazuistika

SOUHRN

Hemofagocytující lymfohistiocytóza je vzácné onemocnění imunitního systému, které postihuje malé děti. Imunitní reakce pacientů je přemrštěná a poškozuje vlastní organismus, takže bez rychle nasazené a adekvátní léčby končí téměř vždy smrtelně. Nemocní nejčastěji trpí vleklou horečkou, zvětšením jater, sleziny a krvácivostí, při laboratorním vyšetření se ukáže pancytopenie, hypertriglyceridémie, hypofibrinogenémie a zvýšení jaterních transamináz. Familiární forma onemocnění se přenáší autosomálně recesivně a dosud jsou známy čtyři příčinné geny. V tomto sdělení popisujeme fatálně končící případ familiární hemofagocytární lymfohistiocytózy u pacientky, prvního dítěte mladých zdravých rodičů, jež byla smíšeným heterozygotem pro mutaci perforinu. Čtyřtýdenní novorozenec, dosud dobře prospívající, byl přijat do nemocnice v moribundním stádiu, podchlazený a se selhávajícími játry. Diagnóza byla stanovena pitvou a následným genetickým vyšetřením. O pět měsíců později bylo prenatálně potvrzeno, že sourozenec zemřelé je zdravým přenašečem choroby. Tato rodina je dle našich informací teprve druhým případem s potvrzenou mutací genu pro perforin v České repulice.

Klíčová slova: famililární hemofagocytující lymfohistiocytóza – jaterní selhání – hypotermie – novorozenec – prenatální diagnostika

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The condition now termed hemophagocytic lymphohistiocytosis (HLH) was first described as familial hemophagocytic reticulosis in two affected siblings in 1952 (1). HLH is classified into primary (hereditary) and secondary (acquired). Primary HLH is further divided into familial hemophagocytic lymphohistiocytosis (FHLH) and closely related immunodeficiencies which manifest by partial albinism, bleeding, ceroidosis and high susceptibility to HLH (Chediak-Higashi, Heřmanský-Pudlák, Griscelli syndrome). They are transmitted in an autosomal recessive manner. X-linked lymphoproliferative syndrome is another cause of primary HLH in men. Secondary HLH is a reactive condition associated with certain infections, rheumatologic disorders and malignancies. Epstein-Barr virus is the most common cause of infection-associated HLH (formerly virus-associated hemophagocytic syndrome). Viral infection can trigger an attack in genetically predisposed individuals too (2).

The peak incidence of FHLH is between one and six months. 70 – 80 % of patients are below one year of age, however older age groups may be affected including adults (late-onset FHLH). Approximately 10 % manifest in the neonatal period, some immediately after birth or in utero (3). The estimated incidence varies because of uneven geographic distribution. The annual incidence rate of 0.12 – 0.15 per 100 000 children which equals to 1.8 – 2.2 per 100 000 live births was calculated in Sweden (4).

The genetic background is heterogeneous and five disease subtypes have been described (Tab. 1). Approximately one third of FHLH cases are caused by mutations in the perforin gene which maps to 10q22. Since discovery of perforin mutation in 1999, three other causative genes have been identified (5). FHLH type 1 has been linked to chromosome 9 with unknown genetic defect (6). Still 20 – 50 % of involved genes are yet to be explored. Perforin is a pore-forming protein stored in secretory granules of cytotoxic lymphocytes and natural killer (NK) cells. It has an absolutely essential role in granzyme mediated apoptosis of virus-infected and malignant cells. Perforin provides delivery of granzymes into the cytosol of target cells where they

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