Female Gender and Hispanic Ethnicity are Associated with Increased Risk of Subacute Methotrexate Encephalopathy

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Abstract

Subacute methotrexate (MTX) encephalopathy is poorly understood. We performed a historical cohort study of all cases of subacute MTX encephalopathy at Lucile Packard Children's Hospital from January 1, 2005, to December 31, 2011. Of 272 patients receiving MTX, 21 patients were diagnosed with subacute MTX encephalopathy. Nine patients (42.9%) in this study were Hispanic females, whereas Hispanic females represented 56 of 272 (20.6%) total patients (p=0.0084). Further comparison with the 2010 California census confirms a Hispanic female predominance (p=0.032). We report a predominance of Hispanic females with subacute MTX encephalopathy, which suggests a genetic polymorphism that increases disease risk.

Keywords: Methotrexate; Female; Hispanic; Neurotoxicity of therapy

Introduction

Methotrexate (MTX) is a widely used chemotherapeutic agent for the treatment of pediatric malignancies, especially leukemia, lymphoma, and osteosarcoma. MTX use results in varied toxicities that include mucositis, hepatotoxicity, nephrotoxicity, and neurotoxicity. The mechanism(s) that lead to subacute MTX encephalopathy are not well understood. Furthermore, there are few known clinical characteristics, host genotypes, or preceding factors that identify patients at risk. We describe a cohort of patients with subacute MTX encephalopathy treated at Lucile Packard Children's Hospital at Stanford University from 2005 to 2011.

Methods

Institutional review board approval was obtained for this historical cohort study. We defined subacute MTX encephalopathy as described previously in the literature [1-3]. We searched the leukemia (lymphoblastic and myeloblastic), lymphoma (non-Hodgkin's, Hodgkin's), and osteosarcoma databases of Lucile Packard Children's Hospital to identify patients who had subacute MTX encephalopathy from January 1, 2005, to December 31, 2011. We reviewed all patients who developed neurologic symptoms within 2 weeks from MTX therapy. Ethnicities were defined by patient self-identification.

Infant ALL	1
T-cell ALL	1
CNS relapse preB ALL	2
SR ALL	1

Figure 1: Histogram comparisons of gender and race distribution of patients dgnosed with subacute methotrexate encephalopathy at Lucile Packard Children's Hospital. Comparisons demonstrate a predominance of female and Hispanic female subpopulations afected with subacute methotrexate encephalopathy. *p=0.0084, sub-acute methotrexate encephalopathy cohort data (2005-2011) compared with total paediatric leukaemia and lymphoma data at Lucile Packard Children's Hospital (2005-2011) & p=0.032, sub-acute methotrexate encephalopathy cohort data (2005-2011) compared with California paediatric census (2010).

Outcome

Tere was no correlation between length or severity of symptomatology with patient demographics, cumulative MTX dose, or type of preceding MTX exposure. Five patients (23.8%) experienced recurrent symptoms when rechallenged with MTX. All 5 were female, and all recurrences occurred afer intrathecal MTX reintroduction. Of these 5 females, 2 were Hispanic, 2 were Caucasian, and 1 was African American. Tere were no correlations between cumulative MTX dose, timing of MTX reintroduction, and relapse incidence.

Discussion

Subacute MTX encephalopathy is an uncommon treatment complication. It can be disturbing to patients and their families due to the unique neurologic disturbances (e.g., seizures, motor defcits, speech disturbances, and emotional lability). We performed an historical cohort study of patients with this diagnosis to attempt to identify risk factors. Tere are epidemiologic fndings revealed in this patient cohort that have not previously been reported. Compared to the hospital data, there is a predominance of females afected with subacute MTX encephalopathy. Tis fnding is not replicated when compared to the California census data, although it approaches statistical signifcance. Furthermore, though small numbers preclude power for statistical signifcance, it is important to note that all 5 recurrences in this cohort occurred in female patients. Secondly, while Hispanic ethnicity alone was not found to be statistically signifcant, we found there was also a signifcantly increased number of afected Hispanic females, which also was not refective of a predominance of Hispanic females treated at this institution or a predominance of Hispanic females in California.

To the authors' understanding, this is the frst cohort in which there is a predominance of Hispanic female patients. Te underlying pathophysiology of this interaction is not well understood. One speculation is a possible ethnic link to methylenetetrahydrolate reductase (MTHFR) polymorphisms. MTHFR polymorphisms have been linked with acute MTX toxicities, including hepatoxicity, neurotoxicity, nephrotoxicity, and mucositis [5-8]. MTHFR plays a key role in folate metabolism, catalyzing the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. Antimetabolites such as MTX block this enzymatic pathway, resulting in organ toxicities. Te most common MTHFR polymorphism, 677C>T, has been particularly implicated in MTX toxicity [5-8] and 1 case report of subacute MTX encephalopathy [9]. Tis polymorphism has been reported to be of especially high incidence in Hispanics [10-12]. Tis phenomenon may help explain the predominance of afected Hispanics on this cohort, but does not explain the female predominance; this second fnding could interact with the distribution of the polymorphism and warrants future investigation.

One potential confounding reason for the predominance of females reported in this cohort is the relatively high incidence of afected female patients with HR B-ALL treated at this institution. However, from 2005 to 2011, there were 43 total males who had HR B-ALL treated, but only 2 developed subacute MTX-encephalopathy. Alternatively, there were 45 total females who had HR B-ALL treated during this time frame, and 8 developed subacute MTX-encephalopathy. Again this highlights a possible inherent difference between females and males in MTX metabolism and MTX encephalopathy risk.

Tere are potential confounding variables that may contribute to the symptomatology described in this patient cohort. Six patients were exposed to low-dose cytarabine (75mg/square meter) preceding encephalopathy onset; however, cytarabine neurotoxicity presents more commonly with cerebellar symptoms (specifcally ataxia and nystagmus), in patients given high-dose cytarabine (3g/square meter) [13-15]. Furthermore, MRI fndings nding the y. sm aP p ' i orten, J

Conflict of Interest

The authors do not have any conflicts of interest to disclose.

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