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Changes in body weight and height in survivors of Menkes disease

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ABSTRACT

Objective: To explore the changes in the body weight and height of Menkes disease (MNK) patients treated with long-term copper–histidine.
Methods: A survey involving a retrospective review of medical records or summaries of MNK patients was conducted. Patients were 44 males born after 1994, and their feeding method and genetic analysis of the *ATP7A* gene were reviewed. We compared the data of body weight and height from birth until 6 years between classical MNK patients and the general population obtained from national data and between patients who received early treatment and patients who received late treatment.
Results: Although five patients who received early treatment reached some developmental milestones, the body weight and height did not differ from patients who received late treatment in the mode of oral nutrition, and were lower in comparison to the national data (<3 percentile).
Conclusion: We reported changes in the body weight and height of MNK patients who received early and late treatment. Although early treatment with copper–histidine had favorable effects on neurological development, it did not result in improvements in body weight and height. We suggest that the establishment of sufficient nutritional support is necessary along with early parenteral copper treatment to improve whole body condition in MNK patients.

Introduction

Menkes disease (MNK) is an X-linked recessive disorder of copper metabolism, caused by mutations in the *ATP7A* gene (OMIM#300011). This gene is located on chromosome Xq13.3 and encodes ATP7A, a copper-transporting ATPase [1–3]. There are several clinical variants of MNK: classical MNK, mild MNK, and occipital horn syndrome (OHS) [4,5]. Classical MNK presents within the first year of life with kinky hair, seizures, neurodegeneration, and failure to thrive. Furthermore, without adequate treatment, most patients die before the age of 3 years. OHS shows prominent connective tissue abnormalities, pathognomonic occipital exostoses, and mild intellectual impairment from 3 to 10 years of age. Mild MNK lies between classical MNK and OHS and shows developmental delay, variable connective tissue abnormalities, pili torti, and cerebellar ataxia, but without seizures or childhood death. To date, only a few patients with the mild form have been reported [6]. A few female MNK patients were diagnosed having X chromosome abnormalities [7].

Parenteral copper injection, reported in 1993, is the current therapy [8]. Its efficacy is dependent on the age of the first administration, the type of gene mutation, and the function of copper enzymes [9,10]. For example, parenteral copper injection can increase plasma levels of copper and ceruloplasmin, can change hair color to natural black, and can improve patients' muscular tone and seizures. However, the response of abnormalities in connective tissues caused by lysyl oxidase is very poor. In 1998, Christodoulou et al. [11] described the long-term clinical course of four boys who had been treated since early infancy with parenteral copper–histidine, with a follow-up period over 10–20 years. As a result of early treatment, the patients had a normal or near normal intellectual development. The oldest patient was 20 years of age at the time of the report. He had suffered from persistent chronic diarrhea since early infancy [11]. However, there are no reports that

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record changes in body weight and height in MNK patients treated with copper–histidine; therefore, changes in these parameters in such patients remain generally unknown.

The incidence of live-born infants with MNK is 2.8 per million live births in Japan [12]; thus, 3–4 MNK patients are born in Japan annually. In Japan, all residents are covered by at least one health insurance plan and all residents adopt partial cost sharing [13]. Moreover, all patients can receive medical aid even as children to reduce their partial cost sharing [13].

The early signs of MNK are not disease specific, thereby early diagnosis is difficult [12]. However, in families with a proband, prenatal diagnosis could be performed [14]. To estimate the long-term efficacy of treatment with copper–histidine, we aimed to explore the changes in the body weight and height of Japanese MNK patients treated with copper–histidine and to compare these changes between patients who received early and late treatment.

Patients and methods

Study population

The present research was an observational study. A nationwide retrospective survey of MNK and OHS was conducted, which involved sending a questionnaire to pediatricians at the end of 2010. The first survey identified 134 patients diagnosed by board-certified pediatric neurologists in pediatric departments of university and government hospitals and departments of pediatrics at facilities for mentally and physically disabled people. For these 134 patients, a second questionnaire survey was conducted, which included the following items: status of birth, diagnosis, treatment with copper–histidine and anticonvulsants, nutritional intake, change in body weight and height, genetic analysis, and prenatal diagnosis. Data were obtained from medical records or summaries. Of the initial 134 patients, we collected data from 62 patients. According to the Medical Practitioners Act of Japan, medical records must be maintained in medical institutions for only 5 years; therefore, some patients' data were lost. Female patients, OHS or MNK patients who had onset at over 12 months of age, one Brazilian patient, repeat cases, patients without description of growth parameters, and patients born before 1994 when treatment with copper–histidine was not established in Japan were excluded. Therefore, the final study population included 44 male patients who had records of growth parameters and were diagnosed by clinical examination, laboratory data including catecholamine tests, measurement of copper concentrations in cultured cells, and/or genetic analysis [12,14–17]. Of the 44 patients, 37 had been diagnosed by genetic analysis of the *ATP7A* gene. A mutation in the *ATP7A* gene was detected in four of five patients who received early treatment.

All the patients had been referred at least once to the Department of Pediatrics of Teikyo University School of Medicine, Japan, for counseling, copper–histidine therapy, and biochemical (including catecholamine-associated data) and/or molecular pre- and postnatal diagnosis of MNK [12,14–17].

In Japan, copper–histidine is prepared using the same protocol described by Sarkar et al. [18]. Approximately 375 mg/dose of parenterally administered copper–histidine was given three times a week, and adjusted to maintain serum copper and ceruloplasmin levels within a normal range; these were monitored regularly.

We divided the MNK patients into two groups: early treatment and late treatment. Five patients received early treatment and 39 patients received late treatment. The five patients in the early treatment group were diagnosed prenatally and started treatment with copper–histidine within 1 month of birth (Table 1). Patients in the late treatment group were diagnosed and started treatment with copper–histidine more than 1 month after birth (Table 2).

Table 1
Percentiles of body weight and height at birth and during treatment in MNK patients treated with copper–histidine within the first month of life, after prenatal diagnosis.

Nutrition	Patients (mutation in the *ATP7A* gene)	Age (months), status at the time of study	At birth (percentile)		At 1 month health check-up (percentile)		During treatment (percentile)					
			Weight	Height	Weight	Height	Age (months)	Weight	Height	Age (months)	Weight	Height
Oral feeding only	Patient 1 (D1219FS1225X)	35, alive[a]	10–25	10–25	3–10	10–25	6–12	<3	<3	13–32	<3	<3
	Patient 2 (D1305E)	48, alive	10–25	10–25	90–97	50–75		<3	<3	13–36	<3	<3
	Patient 3 (IVS8+6T>C) [16]	84, alive	3–10	–	–	–		<3	<3	24–60	<3	<3
	Patient 4 (no data)	23, dead	3–10	–	–	–		–	–	–	–	–
	Patient 5 (S761FS770X) [16]	84, dead (mean ± SD: alive, 55.7 ± 25.4 (n=3); dead, 53.5 ± 43.1 (n=2))	25–50	10–25	–	–		–	–	56	<3	<10–25

MNK: Menkes disease; SD: standard deviation.
[a] Alive: confirmed alive by October 31, 2013.