Brain & Development 36 (2014) 388–393

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Nationwide survey of Arima syndrome: Revised diagnostic criteria from epidemiological analysis

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Received 31 December 2012; received in revised form 30 May 2013; accepted 3 June 2013

Abstract

Aim: We have never known any epidemiological study of Arima syndrome since it was first described in 1971. To investigate the number of Arima syndrome patients and clarify the clinical differences between Arima syndrome and Joubert syndrome, we performed the first nationwide survey of Arima syndrome, and herein report its results. Furthermore, we revised the diagnostic criteria for Arima syndrome. *Methods:* As a primary survey, we sent out self-administered questionnaires to most of the Japanese hospitals with a pediatric clinic, and facilities for persons with severe motor and intellectual disabilities, inquiring as to the number of patients having symptoms of Arima syndrome, including severe psychomotor delay, agenesis or hypoplasia of cerebellar vermis, renal dysfunction, visual dysfunction and with or without ptosis-like appearance. Next, as the second survey, we sent out detailed clinical questionnaires to the institutes having patients with two or more typical symptoms. *Results:* The response rate of the primary survey was 72.7% of hospitals with pediatric clinic, 63.5% of national hospitals and 66.7% of municipal and private facilities. The number of patients with 5 typical symptoms was 13 and that with 2–4 symptoms was 32. The response rate of the secondary survey was 52% (23 patients). After reviewing clinical features of 23 patients, we identified 7 Arima syndrome patients and 16 Joubert syndrome patients. Progressive renal dysfunction was noticed in all Arima syndrome patients, but in 33% of those with Joubert syndrome. *Conclusion:* It is sometimes difficult to distinguish Arima syndrome from Joubert syndrome. Some clinicians described a patient with Joubert syndrome and its complications of visual dysfunction and renal dysfunction, whose current diagnosis was Arima syndrome. Thus, the diagnosis of the two syndromes may be confused. Here, we revised the diagnostic criteria for Arima syndrome.

Keywords: Arima syndrome; Diagnostic criteria; Epidemiological study; Joubert syndrome; Nationwide survey

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http://dx.doi.org/10.1016/j.braindev.2013.06.005

1. Introduction

Arima syndrome (AS) (OMIM 243910) has been described as an autosomal-recessive-inherited rare disease since 1971. It shows 5 characteristic features; severe psychomotor delay (no gain of meaningful speech and walk alone) from the early infantile period, cerebellar vermis agenesis, renal dysfunction (pathologically nephronophthisis), visual dysfunction and ptosis, and death by renal failure in childhood [1–3]. In addition, pathological characteristics of AS were dysplasia of the ventral parts of the pons and inferior olivary nuclei and hepatic fibrosis [3]. Although these cases demonstrate peculiar symptoms, they are usually diagnosed at a time of progressive renal failure because AS is a very rare disease. Only approximately 10 cases of AS have been reported until now [4–11]. Thus, AS is a very rare disease, and its clinical features remain largely unknown. Dekaban syndrome has been described as similar phenotypes of AS [12]. However, AS is readily distinguished from Dekaban syndrome, given the severity of psychomotor development and ptosis [13].

Cilia are microtubule-based appendages, which are detected in most vertebral cells. Among them, motile cilium has two central microtubules ($9 + 2$ structure) and makes fluid flow to form the body axis at the early embryonic period. In contrast, primary cilium, which has no central microtubule ($9 + 0$ structure), recently has been known as sensory organella, which become the origin of intracellularly physiological and chemical signals [14]. Because of their importance for developmental signaling pathway, their dysfunction causes abnormalities in neural tube closure, skeletal defects such as polydactyly, cystic kidney, liver and/or pancreatic diseases, blindness or anosmia, behavioral and/or cognitive defects, and obesity [14,15]. Those are so-called ciliopathy. Recently, some neurodevelopmental disorders of the ciliopathies commonly include the symptoms of severe psychomotor delay, cerebellar vermis agenesis and cystic kidney [16,17]. They consist of Joubert syndrome (JS) (OMIM 213300), Senior-Loken syndrome (OMIM 266900), COACH syndrome (OMIM 216360), etc. as JS-related disorders (JSRD). Among them, JS and JSRD are described as having causative genes of AHI1, NPHP1, NPHP6 (CEP290), TMEM67 (MKS3 or MECKELIN) and RPGRIP1L [17,18]. Of course, these genes are related to dysfunction of the primary cilia. On the other hand, the causative genes of the other syndromes and AS have been never known.

In the present study, we performed the first nationwide survey of AS and revealed the clinical characteristics for making diagnoses. Furthermore, we proposed revised clinical criteria of AS and discussed the relationship between AS and the ciliopathy.

2. Methods

Under the ethical principles of epidemiological study from the Ministry of Education, Sports, Culture and Technology, and the Ministry of Health, Welfare and Labor in Japan, and with the permission of the ethical committee of the Tokyo Metropolitan Tobu Medical Center for Persons with Developmental and Multiple Disabilities, we sent out all questionnaires and performed analyses of the responses.

First, to investigate the number of patients with AS in Japan [1–3], we sent the primary questionnaire to all 483 hospitals with a pediatric clinic, 74 national hospitals and 120 municipal and private facilities for persons with severe motor and intellectual disabilities (SMID). The primary questionnaire asked the number of patients with the following A and B phenotypes and more; 5 typical symptoms of (A) severe psychomotor delay, (B) cerebellar vermis agenesis, (C) hypo-osmolality of urine and progressive renal dysfunction from the childhood (occasionally appearance of cystic kidney), (D) congenital visual dysfunction and (E) peculiar face with ptosis [1]. JS and JSRD are known as a disease similar to AS. We also confirmed JS, whose diagnostic criteria included the previous description [19], from the responses. The secondary questionnaire, including the detailed clinical course, pathology and genetic examination, was sent to the first hospitals that responded to the primary questionnaire. All studies were performed from June, 2010 to March, 2011.

3. Results

3.1. Primary survey

The response rate of the primary survey was 72.7% from hospitals with a pediatric clinic, 63.5% of national hospitals and 66.7% of municipal and private facilities for persons with SMID. We obtained the questionnaire responses from 33 hospitals or facilities. The number of patients with 5 typical symptoms was 13, and that with 2 or more symptoms was 32.

3.2. Secondary survey

The response rate of the secondary survey was 52%, consisting of 23 patients from 17 hospitals or facilities. We received only 23 patient responses, among 32 of the primary survey. After we reviewed the clinical features of these 23 patients in detail, we identified 7 of them with AS and 16 with JS (Table 1). We corrected the number of patients to omit double-registration with the second responses. The patients, having all 5 symptoms were diagnosed with AS, whereas the patients with 2–4 symptoms were diagnosed with JS (Table 1). JS patients had never shown all 5 symptoms. It is important for