Commentary

A tribute to Keiko Kobayashi and her work on citrin deficiency

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Associate Professor Keiko Kobayashi from Kagoshima University, together with Professor Takeyori Saheki, was the pioneer in the field of research on citrin deficiency.

Since her medical graduation and subsequent obtainment of her PhD at Tokushima University, Japan, Associate Professor Kobayashi had been involved in the field of biochemical and molecular genetics—her early interest had been in the study of the molecular mechanism on the heterogeneous distribution of argininosuccinate synthetase in the liver of type II citrullinemia in 1986 [1]. This led to further research in the 1990s culminating in the characterization of the gene involved in citrin deficiency [2]. Together with Professor Saheki and their collaborators, they identified two phenotypes of citrin deficiency: citrullinemia type II (CTLN2) and neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) and delineated the involvement of the aspartate-glutamate carrier for urea synthesis and maintenance of the urea cycle [3].

She and her team had worked on all aspects of citrin deficiency, ranging from the basic sciences to epidemiology aspects as well as the clinical and molecular heterogeneity of the condition [4–6], development of mouse models [7] as well as formulating the treatment options for citrin deficiency [8].

Associate Professor Kobayashi and her team faced a number of challenges. First, there was a perception that citrin deficiency was found mostly in Japanese and East Asians only. However, as a result of the availability of genetic testing of the SLC25A13 gene, this led to the earlier diagnosis of NICCD and the benefits included avoidance of extensive and potentially risky investigations in infants with neonatal cholestasis, provision of appropriate dietary management and genetic counseling, and long term health surveillance [5]. In many centers in Asia and elsewhere, NICCD is a condition to be excluded early in infants with prolonged cholestasis and this had led to a change in pediatric practice.

The awareness that biochemical changes may be absent in NICCD led to the need to develop a cost effective technique for molecular diagnosis in the population. This approach has been taken to the next step whereby mass screening of common mutations found in the population is now developed. This can potentially be used in expanded newborn screening programs [10,11].

In addition to the probands, other family members with NICCD were identified using this approach. Undoubtedly, many lives were saved as a result. Prenatal diagnosis for this condition had also been successfully carried out [12].

Throughout the past decade, many medical geneticists, particularly those from third world countries with limited resources, had found Associate Professor Kobayashi to be pleasant, helpful and compassionate. She was ever constructive in her comments and careful about the accuracy of clinical and laboratory data. It was truly educational and an eye-opening experience to collaborate with her and her team. Not many people were aware she had been unwell for some time. In person, she was always humble, encouraging and positive.

In honor of her work and achievements, the Asian Society for Inherited Metabolic Diseases (ASIMD) during the First Asian Congress for Inherited Metabolic Diseases (ACIMD) in Fukuoka, Japan, 7th–10th March 2010 organized a symposium on ‘citrin deficiency’ where several key researchers were invited to give talks. In December 2010, the Asia-Pacific Society of Human Genetics organized a workshop during the 9th Asia-Pacific Conference on Human Genetics entitled AASPP Symposium on Citrin Deficiency on the 2nd December 2010. She delivered the first lecture entitled “SLC25A13 Mutations/Variations in Citrin Deficiency: Frequency and Distribution”.

She passed away peacefully several weeks later at the age of 63 years old. She had touched countless lives of her patients, colleagues and peers. She had inspired a generation of young geneticists particularly from Japan and Asia that much work remains to be done, both in citrin deficiency, in particular and in inherited metabolic disorders, in general. She was a dedicated teacher, mentor and friend and shall be greatly missed.

References


