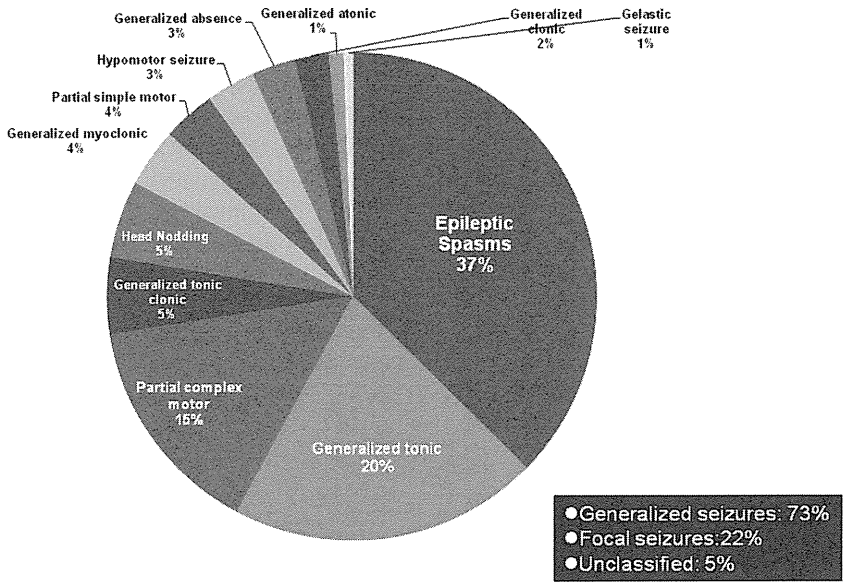

Fig. 2. Main seizure type classification ($n = 314$). The most frequent seizure type was epileptic spasms (ES), accounting for 37%, followed by GTS at 20%, and partial complex motor seizures at 15%. ES and GTS were the main seizure types in at least 57% of all patients.

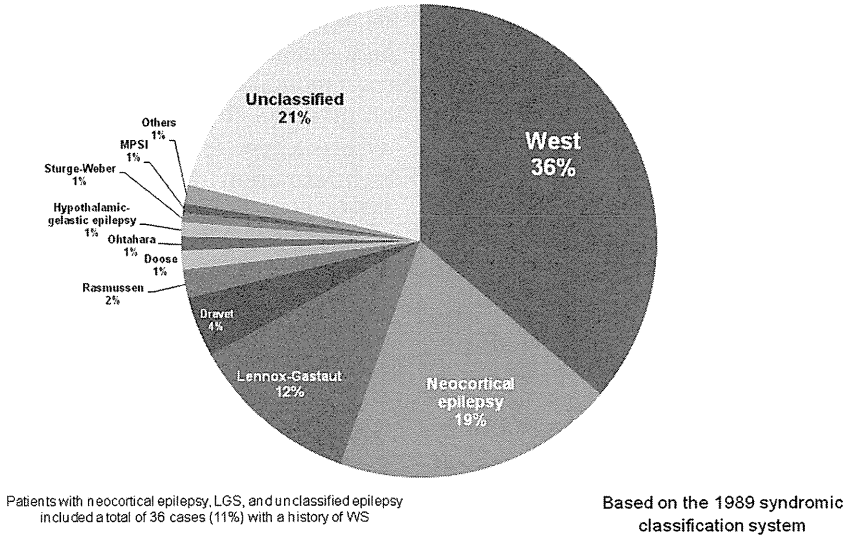

Fig. 3. Epilepsy syndromic classification at the time of the investigation ($n = 314$). The most frequent epileptic syndrome was West syndrome, which accounted for 36%, followed by unclassified epilepsy at 21%, neocortical epilepsy at 19%, and others. Patients with neocortical epilepsy, LGS, and unclassified epilepsy included a total of 36 cases (11%) with a history of WS.

15%, and tuberous sclerosis for 10%. However, etiology is still unknown in the remaining 40% of patients.

4.4. Psychomotor development

There were only two patients who were able to undergo Tanaka-Binet Japan-made IQ tests (IQ values: 65, 47). Thus, these two patients were judged to have mild and moderate retardation, respectively. The remaining 312 patients underwent psychomotor assessment. Among them, psychomotor development at the time of the first examination was normal in 15% of all patients, borderline to mild retardation in 23%, moderate retardation in 18%, severe retardation in 16%, and severe disabling in 28%. Thus, 38% of patients achieved normal to mild psychomotor development, while 62% exhibited already worse than moderate retardation at the time of the investigation.

Discussion

This study was the first multi-institutional collaborative study prospectively investigating many children with catastrophic epilepsy that developed at an age younger than 6 years old. The definition of catastrophic epilepsy was referred from other studies [3,12,13] and

had its own criteria of more than 10 seizures/month refractory to more than two antiepileptic drugs and ACTH therapy, resulting in the stagnation/deterioration of psychomotor development. Although it was arbitrary, this definition could cover the vast majority of refractory epilepsy syndromes as shown in the syndromic classification.

This large cohort study demonstrated that WS was the most frequent cause of catastrophic epilepsy in infancy and early childhood. In general, ACTH and various antiepileptic drugs have been administered to patients with WS, and have achieved long-term epilepsy remission in approximately half of these patients [14–17]. However, the remaining patients were mostly left with intractable epilepsy, often evolving to LGS and neocortical focal epilepsy, and also moderate to severe mental retardation. In this study, a total of 149 cases or 47% of all cases were classified either into WS or epilepsy with a history of WS. Oka et al. carried out an epidemiological survey in childhood epilepsy in Okayama prefecture in Japan and demonstrated that WS was the most frequent epileptic syndrome, accounting for 4.93% of all patients with epilepsy aged 1 month to 13 years of age [18]. This figure was 8-, 6.6-, and 62-times larger than the prevalence of LGS, and Dravet and Doose syndromes, three major representative intractable epileptic syndromes during early childhood, respectively.

The third largest group was neocortical epilepsy, accounting for 19%. More than two thirds of patients developed focal seizures younger than 12 months old. In this age range, the most severe epilepsy was most likely to develop in the form of diffuse epileptic encephalopathy irrespective of etiology. However, we previously reported that catastrophic focal epilepsy in patients less than 12 months old was characterized by multifocal seizure onsets and deleterious clinical courses with numerous focal seizures caused in part by metabolic/structural abnormalities [19].

As for the most disabling seizure type shown in 314 patients, ES and GTS, accounting for 42% and 20%, respectively, were the two most important seizure types, corresponding to both WS and LGS, respectively. The epilepsy onset age in 75% of all cases was 1 year or less when symptomatic epilepsy outnumbered idiopathic or cryptogenic epilepsy. Psychomotor development was already worse than a moderate degree in nearly two thirds of these patients at the time of investigation, which was not contradictory to the outcomes of WS, especially symptomatic outcomes [14,16,17,20].

A few studies investigated seizures in the first year of life excluding febrile seizures, and all of these demonstrated that WS cases accounted for nearly 50% of cases and seizure as well as intellectual outcomes were grave, not only in cases with WS but also in those with other seizure types [21–23]. In pediatric surgical series, one large ILAE-based cohort study investigating 543 children undergoing epilepsy surgery (age: 0–18 years) showed that the age at seizure onset was 1 year or less in 46% of patients, which increased up to 68% if patients were younger than 3 years. In this study, the most frequent etiologies were cortical dysplasia (42%), tumors (19%), atrophic lesions, and strokes (10%) [24]. In another report studying 116 patients undergoing epilepsy surgery in the first 3 years of life, the result was more distinct that the seizure onset was in the first year of life in 82% and the most frequent cause was a malformation in cortical development (49%), followed by tumors (19%) [25]. Although surgical series were biased to those with localized or hemispheric cortical lesions, they included those with true catastrophic cases.

In our cohort, cortical dysplasia and chromosomal anomalies were also two of the most frequent causes, although other causes were still unknown in nearly one half of all patients. Chugani et al. described that cortical dysplasia was found in many patients who underwent respective surgery based on PET despite the absence of recognizable MRI focus [1]. Cortical dysplasia type 1 has been recently shown to produce subtle high signal intensities and reductions in the volume of corresponding white matter only [26–30]. Most cases of unknown etiology may have been caused by cortical dysplasia type 1, which is difficult to visualize even with high-resolution MRI, and only repeated follow-up MRIs may demonstrate subtle white matter changes underlying a dysplastic cortex [31].

Epilepsy surgery for catastrophic epilepsy in children has been steadily increasing in not only the USA but also in the EU, Japan, and other Asian countries owing to the prevalence of neuroimaging modalities. Jonas et al. reported the most recent findings regarding the effectiveness of epilepsy surgery on children with either active infantile spasms (IS) or those with treated IS in whom epilepsy already evolved to other epilepsy types [32]. That study demonstrated a seizure-free rate of 62.5% at 1 year and 44.0% at 5 years, and 80.0% at 1 year and 36.4% at 5 years, respectively. Recently, Baba et al. also attempted corpus callosotomy in 51 infants with active and remote WS aged 24.4 months on average, and demonstrated a spasm-free rate of 33.3%, which represented more than an 80% reduction in spasms in 19.6% of infants, and more than a 50% reduction in 25.8% of infants [33]. These surgical procedures brought about not only seizure reductions but also improvements in psychomotor development.

In conclusion, the most frequent catastrophic epilepsy in infancy and early childhood of less than 6 years of age was WS and its related epilepsy, followed by neocortical epilepsy. Pharmacological and surgical treatments of these patients remain challenging [5,34]. We have to focus on identifying the underlying mechanisms involved and clearly visualize epileptic lesions in these

patients in order to develop new treatment strategies, thereby reducing the number of catastrophic epilepsy patients. Although our study has limitations associated with hospital-based multi-institutional investigations, these results should to be useful in further research to challenge catastrophic epilepsies in young children.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.braindev.2013.02.004.

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