Modern Otology and Neurotology

Makiko Kaga
Kimitaka Kaga

Landau-Kleffner Syndrome and Central Auditory Disorders in Children

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Preface

The author has long been fascinated by the "mysterious" symptoms of Landau–Kleffner syndrome (LKS). LKS was named in honor of Drs. William Landau and Frank Kleffner. It was a chance encounter with patients with LKS who were the patients of the late Dr. Masaki Suzuki (1930–1976). Dr. Suzuki was a child neurologist who was interested in neuropsychology and neuropsychiatry in children. He was one of my mentors in my professional life as a child neurologist. However, he was my teacher only for a year and a half, and he passed away all of a sudden at 46 years of age.

When I first met children with LKS, their diagnosis was "acquired aphasia in children with markedly epileptic abnormal electroencephalogram." Their sequential symptoms of aphasia, auditory agnosia, and word deafness without apparent organic brain lesions simply surprised me. Usually these symptoms of higher cortical dysfunction cannot occur with responsible brain lesions. During their long-term follow-up, most patients fully recovered without apparent handicaps. They spend their lives as the typically developed children/adults. I was again surprised that almost all patients lost their musical ability and such a state continued thereafter even after they became free of auditory verbal symptoms. Moreover, there are some children with incomplete or scarce recovery. I have known and have been impressed by a lady who had a severe sequela of auditory agnosia for more than 50 years. Her efforts to overcome and at the same time to live together with her handicaps is worthy of special mention.

In this book, I tried to show the clinical features of LKS mainly from the viewpoint of auditory agnosia which is the central auditory dysfunction.

Thus, the book is for auditory agnosia and related central auditory dysfunction in children. Part I of this book is just for LKS which is a disease of functional abnormality and was written by Makiko Kaga.

Part II of this book is for the diseases which can manifest central auditory dysfunction due to organic brain lesions. This part was divided up between Makiko Kaga and Kimitaka Kaga. Kimitaka Kaga is an otorhinolaryngologist and is deeply engaged in both peripheral and central auditory dysfunctions in all generations.

We plan to put this book to help diagnosing and treating the rare condition of auditory agnosia in children induced by LKS and other diseases which may develop central auditory dysfunction and are difficult to diagnose. These patients need to be treated and supported for a rather long time.

I appreciate Masaki Suzuki, MD, PhD (1930–1976); Isabelle Rapin, MD (1927–2017); Thiery Deonna, MD; Yoshisato Tanaka, MD, PhD; and Masataka Arima, MD, PhD, for inspiring me about LKS, language development, hearing impairment, neurodevelopmental disorders, and childhood higher cortical functions.

I acknowledge Drs. Osamu Kanazawa, MD, PhD; Shunichi Kato, MD, PhD; Koji Kato, MD, PhD; Hirokazu Oguni, MD, PhD; Norio Sakuragawa, MD, PhD; Masayuki Shimohira, MD, PhD; and Nobuyuki Shimozawa, MD, PhD, for referring patients.

We thank our colleagues, Masumi Inagaki, MD, PhD; Atsuko Gunji, PhD; Kotoe Sakihara, PhD; Wakana Furushima, MD, PhD; Seiko Suzuki, MD, PhD; Toshihiro Horiguchi, PhD; Yoshimi S Kaga, MD, PhD; Takayuki Hatori, MD, PhD; Shingo Oana, MD, PhD; Kyoko Sasaki MD; Naomi Kokubo, PhD; Tatsuyuki Ohto, MD, PhD; Miho Nakamura, MD, PhD; Tatsuya Koeda, MD, PhD; Kenji Sugai, MD, PhD; Takashi Saito, MD, PhD; Hitomi Noguchi, MD, PhD; Mitsuko Shindo, PhD; Masako Nakamura, MS; Reiko Ohta, BS; and Kayoko Sekiguchi, BS.

This book contains the results of Research Grant of Encouragement of Scientists in 2009 from the Ministry of Health, Labor and Welfare, Japan, “Present a real picture of Landau–Kleffner syndrome” (Chief scientist: Makiko Kaga).

In this research project, we thank the Directors of Pediatrics in all Japanese Hospitals which had pediatric departments, councilors of the Japanese Society of Child Neurology, and councilors of the Japan Epilepsy Society for cooperating with the nationwide survey of Landau–Kleffner syndrome.

I appreciate Keiko Okawara, BA, for her marked contribution to prepare this book.

I acknowledge all patients and their families for their cooperation and for teaching us too many things about higher cortical function in children.

Finally, we highly acknowledge Dominic Hughes, PhD, who was so kind to review and correct our manuscript as a smart scientist and a native English speaker.

Tokyo, Japan Makiko Kaga

Contents

Chapter 1
Introduction

It is very difficult to make a correct diagnosis of central auditory dysfunction in children. Even in adults, auditory agnosia is often misdiagnosed probably because its occurrence is very low. Most central auditory dysfunction in adult patients is due to bilateral temporal damage usually caused by cerebral bleeding or infarction.

However, the rarity of this symptom leads to delays in precise diagnosis. The incidence of this dysfunction in children is extremely low compared to adults, and underlying diseases are frequently different from those of adults. It has been reported that herpes encephalitis (Kaga et al. 2000; Kaga et al. 2003) and adrenoleukodystrophy (ALD) (Kaga et al. 1980; Furushima et al. 2015) both underlie the development of auditory agnosia in children. Other than herpes encephalitis, encephalitis/encephalopathy of unknown origin may also uncommonly produce symptoms similar to auditory agnosia (Awaya 1989; Awaya and Fukuyama 1986; Fukuyama et al. 1989). The Landau–Kleffner syndrome (LKS) is the most well-known and is a typical disease which brings on auditory agnosia in children as a functional abnormality.

LKS is named after two authors of this syndrome described in *Neurology* in 1957 by Dr. William Landau (October 10, 1924–November 2, 2017) and Dr. Frank Kleffner (Oct 10, 1925–June 12, 2015) (Landau and Kleffner 1957). Dr. Landau was a young internist/neurologist and Dr. Kleffner was a speech pathologist who had long worked with children who had delayed speech and language disorders in the Institute for the Deaf, Washington University (Kleffner and Landau 2009). Their clinical observations led us to the gateway to LKS's mysterious world. LKS has two major aspects. One is peculiar auditory verbal symptoms and the other is epileptic disorders. Many specialists, such as child neurologists, neuropsychologists, audiologists, and epileptologists, have been interested in this disease. However, the incidence of this disease is very low and even the above-mentioned specialists rarely encounter patients with LKS, therefore once they see an LKS patient they were customarily focusing on the patient's symptoms mainly related to their specialties. Neurologists, speech therapists, and audiologists are fascinated with auditory verbal symptoms whereas child neurologists and epileptologists focused their attention

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onto clinical seizures and subclinical epilepsy. Thus, each expert has evaluated the patient's symptoms as related to his/her own specialty.

In the first part of this book, I will try to open the door to the world of LKS and to explain the disease which manifests auditory agnosia as the central auditory dysfunction coincident with or without epileptic disorders.

In the second part of this book, we will show some pediatric neurological diseases which can cause auditory agnosia as their clinical symptoms. They are ALD, cerebrovascular disease, Herpes and unknown viral encephalitis/encephalopathy, Pelizaeus-Merzbacher disease, hydrocephalus, and brain malformation. Auditory neuropathy/auditory nerve disease (AN) (Starr A et al. 1996; Kaga K et al. 1996) often shows the clinical symptoms similar to auditory agnosia (Kaga M et al. 2002) but its lesion is peripheral and not central auditory cortex, therefore we did not include AN in this book. Thus in this chapter, above diseases will be shown by describing typical case histories.

Again, central auditory dysfunction in children is an extremely rare and unexpected encounter. Consequently, patients may often have received an inadequate or incorrect diagnosis. Therefore, we think that it is important to explain the techniques of correct diagnosis and methods of treatment of these patients to better care for and support them. With the knowledge of pioneers and my experiences as a pediatrician and child neurologist, I will try to illuminate the world of LKS in the following pages. Since I have been fascinated with auditory agnosia in children, my interests have never been failing. You are going to enter the world of LKS with auditory agnosia in children. After putting down this book, I hope that you will support these patients with their long-lasting and invisible sequelae.

The author made two nationwide surveys in 2009 as a research project sponsored by the Ministry of Health, Labor and Welfare of Japan. These surveys were an epidemiological study of auditory agnosia (Project A) and a compilation of its clinical features (Project B). The methods and results of this study are described in later chapters (Kaga 2010).

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Part I
Landau-Kleffner Syndrome (LKS)

Chapter 2
History of LKS and Its Epidemiology

2.1 History of LKS

As mentioned in the introduction, the first report of LKS was published in *Neurology* in 1957 by Drs. William Landau and Frank Kleffner (Fig. 2.1) (Landau and Kleffner 1957). Their case reports included two boys and four girls, aged 5–7 years. The onset of their disease was from 4 to 8 years of age. They were referred to a center for hearing-disabled children. Typical symptoms were receptive language disorder. At the early stage of their disease, the children were thought to have had hearing impairment. Then most of these children became mute and although some could speak, their pronunciation and intonation became unusual like non-native speakers. Moreover, they did not seem to understand the content of conversations. Their mental and language development before disease onset was usually completely normal or even superior. Deterioration of verbal ability and epileptic seizures developed in most of these children around several months before or after their auditory verbal symptoms appeared. Electroencephalographic recordings revealed frequent diffuse spikes or spikes and waves. Temporal or central paroxysms or slow-wave activities were often observed. However, the foci of these abnormalities differed across these children. Auditory verbal symptoms and epileptic seizures were occasionally resolved simultaneously or separately. In most of these children, epileptic seizures were often controlled before complete recovery of their auditory language symptoms. Responses to anticonvulsants were good for their seizures but not for their auditory verbal symptoms. Five among Landau and Kleffner's six patients showed repeated exacerbations and remissions. Speech therapy and education at a special school was administered to five patients. One pair of siblings was included in this initial report.

According to the Kleffner's anecdotal description, he wondered why Dr. Landau was so surprised by the presence of such children (Kleffner and Landau 2009).

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Syndrome of Acquired Aphasia with Convulsive Disorder in Children

William M. Landau, M.D. and Frank R. Kleffner, Ph.D.

CERTAIN OF THE CHILDREN who are evaluated and taught at the Central Institute for the Deaf are classified as aphasic because they present a specific deficit in the ability to use speech and language.[1] For most of these children the deficit seems to be congenital, since they have failed to acquire the ability to use speech and language normally.[2] Some of them, however, have acquired the ability to use language in an apparently normal fashion and have subsequently lost it. Six such children have been seen in the last two years. One of the six became aphasic and hemiplegic after a severe head injury; the remaining five developed aphasia in relation to a convulsive disorder. These five cases are reported here.

CASE HISTORIES

Case 1. A white male, third of four children, was born in April 1948. Pregnancy and birth history were unremarkable. He was a healthy infant, sat at about six months, and walked before he was a year old. He learned to talk normally at 15 to 18 months. Further behavioral development was also unremarkable. In 1952 when the boy was four, he had one nocturnal generalized seizure. When he was five (July 1953), he developed several furuncles over his face. A few days later he fell in the yard and was found in a semiconscious condition. He staggered into the house and vomited several times. Following treatment with penicillin, it became apparent to the family that the child was having difficulty understanding what was said to him, a defect interpreted as "plain stubbornness." His speech also became garbled.

He was hospitalized in August 1953. His electroencephalogram (figure 1A) showed a generalized spike dysrhythmia, most prominent in the temporal leads bilaterally. Neurologic examination was not remarkable except for the deficit in speech. He was considered to have an aphasic disorder, primarily receptive. Three lumbar punctures revealed two white cells and one red cell per cu. mm.; glucose, 47 mg. per cent; protein, 16 mg. per cent; chloride, 112 mEq. per cent; Lange, negative; Wassermann, negative. The patient was given Dilantin and phenobarbital medication and the seizures were controlled.

When he was first seen at the Central Institute for the Deaf in October 1953, he showed very little use or understanding of speech. His hearing seemed unimpaired. Formal auditory tests were not given since he responded quickly and consistently to a variety of soft sounds. He behaved in a stable and intelligent fashion, although he was clearly frustrated by his difficulties in understanding and using speech. Arrangements were made to have him attend the speech clinic; however, two weeks later the mother called and reported that the child was speaking and understanding normally and that he had been admitted to kindergarten. A repeat electroencephalogram at this time (figure 1B) showed no significant change except that the temporal spikes were somewhat more prominent on the left.

Five months later (March 1954) he had a seizure, with unconsciousness and with clonic jerking in the right hand and arm. In July 1954 he had twitching in his right face, looked pale, and went to sleep. During the rest of the summer he had several episodes of twitching of his right face. He would grab at his right cheek and then sit and rest. On one occasion he said that he was nervous. On other occasions he would take off his right shoe to see if his foot were injured and say, "It feels like my nerves." That fall, during a period of about a week, his comprehension and production of speech diminished rapidly to a level worse than that in 1953. There were no obvious seizures at this time.

In December 1954 he was seen in the pediatric clinic. An electroencephalogram again showed a

From the division of neurology and the Beaumont-May Institute of Neurology, Washington University School of Medicine, and the division of speech pathology and speech correction, Central Institute for the Deaf, St. Louis, Missouri.

Fig. 2.1 The first page of the original paper written by Landau W and Kleffner F in 1957. From Landau WM, Kleffner FR. Syndrome of acquired aphasia with convulsive disorder in children. 1957. Neurology 51:1241–8. 1998

Because Dr. Kleffner had seen many children, at his facility for children with deafness and communication disorders, who had lost their speech in that way. He had abundant experience as a therapist of language development and hearing impairment.

With regard to older reports than that of Landau and Kleffner, Kellermann mentioned that Pötzl had already published in German, in 1926, a paper of a patient who had the same symptoms as LKS (Kellermann 1978; Pötzl 1926). That patient presented with the clinical picture of episodic remissions and exacerbations and had epilepsy.

Pötzl's article (Fig. 2.2) was a report of a boy named Otto, aged 7 years (Pötzl 1926). Otto was the son of a doctor and his mother first noted that he did not seem to hear even when presented with loud speech. He lost his speech but initially he understood questions. He had normal physical findings and no suspected preceding events. His clinical history from January to October 1925 was fully described and

(Aus der Prager deutschen psychiatrischen Klinik.)

Über sensorische Aphasie im Kindesalter.

Von
Prof. O. Pötzl,
Vorstand der Klinik.

(Eingegangen am 13. November 1925.)

Die sensorische Aphasie im Kindesalter ist bisher noch wenig studiert worden in Bezug auf die Eigenheiten, die sie von den sensorisch-aphasischen Störungen des Erwachsenen unterscheiden. Der Grund dafür ist vor allem der, daß gerade die sensorische Aphasie im Kindesalter eine recht seltene Erscheinung ist, wie alle Autoren (*Gutzmann*, *Nadoleczny* u. a.) übereinstimmend hervorheben. Überdies sind die an sich seltenen Fälle, in denen eine *sensorische* Aphasie zusammen mit Infektionskrankheiten des Kindesalters aufgetreten ist, in ihren Einzelheiten wenig beachtet worden: sie sind wahrscheinlich für ein Studium einzelner Reaktionen nicht allzu geeignet gewesen. Eine Anzahl anderer Beobachtungen von sensorischer Aphasie im Kindesalter (Fälle von *Schwendt* und *Wagner*, *von Gutzmann*) betreffen *Entwicklungshemmungen* mit dauernder Sprachtaubheit; sie unterscheiden sich mithin schon von vornherein sehr von den Verhältnissen, die eine sensorische Aphasie beim Erwachsenen bedingen. Es ist darum vor allem der Seltenheit wegen geboten, solche Fälle von sensorischer Aphasie im Kindesalter mitzuteilen, deren Bild und Verlauf sich einer sensorischen Aphasie des Erwachsenen soweit annähert, daß eine vergleichende Betrachtung möglich ist.

Fig. 2.2 The first page of the possible oldest article in the world written by Pötzl O in 1926. From Pötzl O. Über sensorische Aphasie in Kindesalter. Z. Hal-, Nasen- und Ohrenheilk 14:190–216. 1926

his clinical symptoms were word deafness and sensory aphasia. The progress of his exacerbations and improvement in his conversational ability at the doctor's office was precisely recorded. Speech therapy was initiated and Dr. Pötzl reported it as being effective. Although Dr. Pötzl did not mention epilepsy or epileptic episodes in his report, his described scenario of Otto's clinical progression was quite similar to that of LKS. Following his clinical report, Pötzl discussed in detail the possible lesions underlying aphasia and furthermore he attempted to elucidate the difference between aphasia in children versus in adults. This remains to be an interesting academic issue even now. He also mentioned amusia in relation to aphasia.

Year 1926 (Pötzl's date of publication) was prior to the report of the discovery of human EEG by Hans Berger in 1929. However, Wernicke's sensory aphasia, Broca's motor aphasia, and the concept of cortical/subcortical aphasia had already been thoroughly discussed in the literature (Pötzl 1926). It would not be surprising if LKS would subsequently be renamed as the Pötzl–Landau–Kleffner syndrome.

Following the initial publication describing LKS by Landau and Kleffner in 1957, Worster-Drought published, in 1971, a paper entitled "An unusual form of acquired aphasia in children" (Worster-Drought 1971). This paper reported the findings of 14 patients with acute epileptic electroencephalographic abnormalities. Of these patients, some failed to completely recover from their verbal symptoms. In the same year (1971) Suzuki reported a case of 4-year-old Japanese girl with acquired aphasia and he provided findings of his extensive neuropsychological workup of her in "Acquired sensory aphasia, a case report" (Fig 2.3). This paper was not widely read outside of Japan in that it was written in Japanese. Because of her sequela of auditory agnosia, Dr. Suzuki and I have been following up with this patient for more than 49 years (Kaga et al. 2016). In 1973, Gascon published an article "Language disorder, convulsive disorder and electroencephalographic abnormalities. Acquired syndrome in children" which described three patients with incomplete recovery of both their epilepsy and their verbal difficulties. In 1974, Shoumaker et al. published their study of three patients, 5–6 years of age. One of the patients had no clinical documented epilepsy. The paper was entitled "Clinical and EEG manifestation of an unusual aphasic syndrome in children". In the same year, 1974, McKinney et al. also described nine patients under care at the Hospital for Sick Children in Toronto, Canada. The article is titled "An aphasic syndrome in children" (McKinney and McGreal 1974). Subsequent to McKinney's article, eight articles relating to LKS quickly appeared in the literature: Deuel et al.; Lou et al.; Deonna et al.; Rapin et al., and Foerester separately published an LKS article in 1997 (Deuel and Lenn 1977; Lou et al. 1977; Deonna et al. 1977; Rapin et al. 1977; Foerster 1977). Although most of the above review articles were presented as case reports of those authors' patients, with discussions of previously published reports, Rapin tried to explain the mechanism of auditory verbal dysfunction in LKS with her description of five new patients in her paper, "Verbal auditory agnosia in children". Tanaka also presented "Three patients with auditory agnosia in childhood", but it was written only in Japanese (Tanaka and Kaga 1977). He pointed out that those patients' symptomatology was consistent with auditory verbal agnosia. In 1978, more case reports of LKS appeared in the literature: Cooper et al., Kellermann, and van Harskamp et al.

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後天性感覚性失語症の一幼児例

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Acquired Sensory Aphasia, A Case Report

Masaki Suzuki, M. D. and Keiko Takeuchi, M. D.
(Department of Pediatrics, University of Tokyo)

A case of a girl with acquired sensory aphasia of obscure origin was reported. Her family history was noncontributory and physical and mental development was almost normal until the age of 4 years and 7 months, when she developed difficulty in comprehension of spoken language 5 months later of attack of measles. Two days prior to the onset of measles, she was administered on killed measles virus vaccine. Thereafter, spontaneous speech was also lost gradually. No focal neurological abnormalities such as paralysis, agnosia and apraxia were observed and her intelligence seemed to be entirely normal. She was impressed to be very friendly and rather euphoric with anosognosic tendency. Laboratory studies including cerebrospinal fluid, carotid angiography, pneumoencephalography and brain scanning revealed no specific findings. Electroencephalogramm showed right temporal dominant single spike. Repeated audiological examinations revealed almost normal hearing. Recovery of comprehension and expression in speech was very poor, so that special education by written language, and lip reading was commenced. Learning of written language was satisfactory, while lip reading was very diffcult for her. Several problems concerning diagnosis, etiology neurological consideration, and education for the patient were discussed.

Fig. 2.3 The first page of the second or the third oldest article by Suzuki M et al. Suzuki M, Takeuchi K. [Acquired sensory aphasia in a child]. *No to Hattatsu (Brain & Development)* 3:147–58. Japanese. 1971. *No to Hattatsu* is an official of the Japanese Society of Child Neurology

Mantovani and Landau's published a paper in 1980 about the long-term prognosis of LKS which had a crucial influence on the study of this disease. Their paper described nine LKS children, including six original patients from the initial article by Drs. Landau and Kleffner, and showed the importance of clinical follow-up of these patients and outlined the marked differences between their prognoses (Mantovani and Landau 1980; Baynes et al. 1998; Kaga et al. 2016).

In 1980, de Negri summarized his findings of epileptic-aphasia syndrome in eight patients. He described three unique clinical features: (1) critical but transient aphasia; (2) a serious "congenital" condition; (3) acquired aphasia. In 1982, Yashima reported a number of cases of epileptic aphasia syndrome. She classified this transient form of the disease into two groups based on their speech and language symptoms, i.e., a transient good prognosis group and a chronic poor prognosis group

(Yashima et al. 1982). In 1985, Bishop published a review article of 124 acquired aphasia with convulsive disorder (Landau–Kleffner syndrome) patients (abstracted in French, German, and Italian) and she included five of her own patients as well. She compared and analyzed these patients in terms of their age at onset and their prognoses (Bishop 1985). In the same year, Beaumanoir tried to analyze the clinical picture of 131 patients including her one patient (Beaumanoir 1985).

From around 1982, references to the Landau–Kleffner syndrome (named in honor of the authors) and articles reporting findings of this syndrome became quite common in the literature (*Neurology)* thus establishing the name of this syndrome in honor of the authors.

Digressing in time somewhat, in 1971, Patry et al. described and introduced the concept of ESES (electrical status epilepticus during slow-wave sleep) (Patry et al. 1971). Kellermann described the relationship between recurrent aphasia and ESES (Kellermann 1978). Tassinari described the encephalopathy underlying ESES (Tassinari et al. 1977). The term CSWS (continuous spike-wave during slow-wave sleep) has also been used to describe ESES but there exists a controversy as to which term is most accurate.

Kellermann's paper prompted a new emphasis on and new directions in the study of LKS. The number of specialists who regarded electroencephalographic abnormality as the cause of LKS increased and the emphasis of published studies changed from a neuropsychological approach to the study of auditory agnosia and aphasia to reports of studies of electroencephalographic changes and epileptic seizures underlying LKS.

Review articles about the relationship between LKS and ESES/CSWS have been published by Deonna (1991), Jayakar and Seshia (1991), Beaumanoir (1985), Tassinari et al. (2005), and others. The recent trend of thinking seems to be that both the neuropsychological approach and the electroencephalographic approach would, in essence, come to the same end. Patients with ESES occasionally present various cognitive dysfunctions or declines including language disorders. Also, patients presenting with a language dysfunction, including LKS, exhibit ESES on their EEGs. These phenomena are surely observed and considered from both ends. Then the concept of "spectrum disorder" appeared in the literature and it included LKS. Thus, the recent tendency has been to lump these patients together under the rubric of spectrum disorders, from Rolandic epilepsy to the severest form of LKS, because of the similarity of the electroencephalographic features of each.

Recently, I examined a patient who was initially diagnosed with benign Rolandic epilepsy but his diagnosis was subsequently changed to LKS. He indicated that his first symptom was a persistent and generalized tonic–clonic convulsion at night. His EEG revealed limited Rolandic spikes. Two months later his auditory verbal symptoms appeared (reference Patient H in subsequent pages).

It has become apparent that patients with ESES/CSWS who do not exhibit aphasic or auditory agnosia symptoms do not suffer from LKS. In addition, patients with apparent congenital intellectual disability or deterioration also should not be considered as having LKS. However, from the broader sense of electroencephalographic and language symptoms, LKS and Rolandic epilepsy become to be thought of as the

severest and the mildest phenotypes of a spectrum of childhood focal epilepsies (Deonna and Roulet-Perez 2016).

In any case, we are charged with the determination of the common etiology of the seemingly similar phenomena of these patients. New technologies have become available in clinical medicine and every effort has been made to finally delineate the etiology of this disease but yet its etiology is still elusive.

2.2 Epidemiology

Dugas et al., in 1982, pointed out the rarity of Landau–Kleffner syndrome on the basis of the very limited number of such patients seen even in major pediatric hospitals (Dugas et al. 1982). Following that report, the incidence and prevalence in children has not been studied until our survey in Japan (Project A & B).

At the outset of our survey (2009), we proposed that LKS is a rare disease. Our working hypothesis was that all of the patients so surveyed must have been encountered physicians, especially pediatricians, at some stage of their disease because of their peculiar symptoms. We then sent a questionnaire to all 3004 Japanese hospitals that had a department of pediatrics as of March 2009. The questionnaire asked about the number, age (between 5 and 19 years old), and sex of LKS patients who were new patients or who had been under care in those hospitals during the past year (August 2008 to July 2009). Vital statistics of the same year (2008), published by the Ministry of Health, Labor and Welfare, Japan, were referenced to better enumerate the estimated incidence and prevalence of LKS among all children in Japan. The department heads of 1562 pediatric services answered our inquiry (a response rate of 51.9%). Six of these department heads had recent LKS patients aged 6–14 years (5 boys and a girl). Thirty-two patients (22 males and 10 females) with LKS were followed by 26 pediatric departments during this same time period. Among the 32 patients, 23 were found to be 6–19 years old (Table 2.1).

We presupposed that pediatric department heads would accurately respond to our survey if they had seen LKS patients. This is because there will always be a need for updated information regarding the treatment of LKS patients and the understanding that our research will ultimately facilitate this treatment. Thus, it is highly possible

Table 2.1 LKS patients in Japanese hospitals for a year from August 2008 to July 2009

	The number of facilities	The number of patients			The age of patients		
		Boy	Girl	Total	Boy	Girl	Total
New patients at pediatrics	6 (0.13%)[a]	5	1	6	9.2 ± 3.3	7.0	8.8 ± 3.1
Follow-up patients	26 (0.55%)[a,b]	22	10	32	11.9 ± 4.0	15.3 ± 10.8	13.0 ± 7.0

[a]The ratio of the facilities which consulted LKS patients among the total circularized facilities
[b]The number includes patients aged 20 or above

that the department heads who did not respond to our survey did not encounter any LKS patients during the defined survey term.

In the Vital Statistics of Japan, 2009 it was reported that the population of Japanese children between the ages of 5 and 14 years old was 11,861,464 and those between the ages of 5 and 19 years old was 18,007,968 (total population of Japan in 2009 was 127,510,000). From our 1 year survey, we determined that there were only six patients in the age range of 5–14 years who, on their first physician encounter, were diagnosed with LKS. Thus, the occurrence of LKS, within 1 year, should be 6 (up to 11.5 at the most). We thus estimated the incidence of LKS in the 5–14-year age range in the overall Japanese population to be approximately as one in 978,000 people.

Our survey also indicated that the number of children with LKS below the age of 20 and under current medical care was at least 23 and up to 31. Thus, we calculated that LKS patients currently under care and between the ages 5 and 19 years ranged from 44.2 to 59.6 in a population of 18,007,968. This indicates that the prevalence of LKS patients under current medical care and between the ages of 5 and 19 years old is roughly one in 302,147–407,420.

Hence, the incidence of children between the ages of 5 and 14 years old diagnosed with LKS on their initial physician encounter and occurring within 1 year is about one in a million. However, the incidence of children with LKS between the ages of 5 and 19 years and under current medical care was one in about 300,000–410,000 of the Japanese population.

This study was the first epidemiological estimate of the incidence and prevalence of children with LKS in Japan or, for that matter, in any other country.

The limitation of this survey was the lack of data from children under the age of 5 years and which confounded accurate diagnoses.

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Chapter 3
Diagnostic Paradigms

3.1 Clinical Symptoms

The major symptoms of LKS are functional changes in these patients' auditory verbal ability and their EEG findings indicating clinical or occasional subclinical epilepsy. The functional changes consist of receptive aphasia, auditory agnosia, and pure tone deafness. EEG studies are essential in the determination of LKS and often show changes as a result of current or past epileptic episodes. In addition, LKS presents several other psychological symptoms affecting behavior or emotions, especially during onset. We studied those neuropsychological manifestations of LKS during observations in various clinical settings in Japan.

Over a 2-month period, from November 2009 to January 2010, we conducted a secondary survey to further determine the clinical aspects of LKS (Project B). Questionnaires were sent to 400 physicians who were board-certified child neurologists and/or epileptologists (Table 3.1). Most of these physicians were councilors of the Japanese Society of Child Neurology and/or the Japan Epilepsy Society. Those physicians who belonged to both societies were counted as one.

At the outset of this questionnaire, these physicians were divided into two groups: those with experience in treating LKS patients and those who had little or no experience with these patients. Thirty-nine physicians were experienced and the total number of their patients was 65. We carefully monitored for overlaps of the patient

Table 3.1 The respondents of the secondary survey

The number of doctors circularized	400
The number of respondents	133
Male	117
Female	16
Response rate	33.3%

M. Kaga, K. Kaga, *Landau-Kleffner Syndrome and Central Auditory Disorders in Children*, Modern Otology and Neurotology,
https://doi.org/10.1007/978-981-10-1479-6_3

Table 3.2 The number of LKS patients (Project B)

Male patient	35
Female patient	25
Total	60

count. After this monitoring, we determined that the total number of LKS patients who were seen by experienced physicians was 60 (Table 3.2).

We posed additional questions to these 39 LSK experienced physicians. To wit, the number of LKS patients whom they had seen within the past year, these patients clinical signs and symptoms, the time from onset of LKS to diagnosis, the methods of diagnosis and treatment, the patient's types of epilepsy, the time span of observation of each patient, the patients' educational level, how effectively their patients had used the social welfare system, the long-term prognosis of these patients, and whether these physicians had recently contributed articles to the literature related to LKS or had made a presentation of such at an academic meeting.

In the following sections, the details of the clinical symptoms of LSK as gleaned from the literature and from our surveys in Japan (Project B) are described.

3.1.1 Onset of the Disease

Before the onset of LKS, we find that the mental and language development of these patients is essentially normal.

Epileptic seizures are common early symptoms and noted in 60% of these patients. Auditory verbal symptoms may manifest before or after their seizures and these auditory symptoms may include hard of hearing, frequent requests for repetition of presented speech, poor understanding of speech and environmental sounds and abnormal pronunciation or intonation of their speech. Other aspects of the first symptoms of these patients' speech are abnormal verbosity, abnormally careless attitude and/or rude behavior, and general hyperactivity. In most cases, these symptoms gradually increase in severity. Some are initially seen by an otorhinolaryngologist (Tanaka and Kaga 1977; Kale et al. 1995) because they seemed to have become hearing impaired. Only occasionally, were they seen by psychiatrist because of the severe change in their behavior (White and Sreenivasan 1987). A definitive diagnoses of LKS is often made by a child neurologist or an epileptologists based on the clinical symptoms and the EEG findings.

The previous study (Project B explained in the introduction) showed that LKS verbal symptoms have their onset anywhere between 1 year and 7 months to 13 years of age. However, Worster-Drought reported that only two of their patients developed symptoms when they became older than 10 years of age (Worster-Drought 1971). The patients whose symptom onsets were between the ages of 3 and 8 accounted for 85.5% of their total caseload. Broadening the age range to 2–8 years showed that symptom onset increased to 92.8%. Beaumanoir also wrote that 80% of his patients had symptom onsets between the ages of 3 and 8 years (Beaumanoir

1985). Thus, most of the patients in the above-published studies experienced their symptom onsets between 2 and 8 years of age and the peak age range of onset is between 5 and 7 years. Summarizing these studies, the earliest onset of LKS in children was between 18 and 22 months old. The latest onset was between 13 and 14 years of age. The ratio of LKS occurrence between males and females ratio was found to be 2–1.

In our secondary survey (Project B) of Japanese patients, we found that the age of LKS symptom onset was 5.2 years ± 2.9 years (average ± one standard deviation) (Table 3.3) and that symptom of LKS found at their initial physician encounter was 6.7 ± 2.7. The number of males in this last cohort was 35 and the females numbered 25. The male to female ratio was thus 1.4:1. The interval between the time of symptom onset and the first visit was, on average, 1 year and 6 months. In addition, the reporting physicians noted changes in the emotion and behavior of these children occurring either before or after the onset of LKS symptomatology.

The results of our project B survey of the age ranges of early onset LKS symptoms are shown in Table 3.4. Mutism, no response to loud speech, and frequent requests to repeat speech were often noted. Irrelevant answers to questions and

Table 3.3 The patients' age at the onset and the first visit to hospital (Project B)

	The number of patients	The age	
		At the first visit	At the onset
Male	35	6.5 ± 2.4	5.2 ± 2.4
Female	25	6.9 ± 2.9	5.2 ± 3.2
Total	60	6.7 ± 2.7	5.2 ± 2.9

(Average ± SD)

Table 3.4 Early symptoms (Project B)

	Male	Female	Total
Auditory verbal symptoms			
Frequent asking back	7	10	17
No response to a call	14	11	25
Mute	21	18	39
Talkative	0	0	0
Speak nonsense, jargon	4	1	5
Irrelevant answers	6	4	10
Attempt to communicate by gesture	4	5	9
Understand others' gestures	5	0	5
No gestures	0	0	0
Frustrated with communication difficulty	5	7	12
Unconcerned with lack of communication	4	1	5
Epileptic seizures			
Present	33	19	52
Not present	1	3	4

attempts to communicate by gesture also should also be considered as elements of the symptomatology.

Diagnostic tests of LKS, as summarized in our Project B survey, are shown in Table 3.5. EEGs and ABRs were often clinically evaluated. Because our survey responses submitted from university or major hospitals specializing in neurology or epileptology, MRIs, CTs, MEG, and even PET scans were evaluated for most of

Table 3.5 Diagnostic tests in Project B

	Male	Female	Total
Examination	20	16	36
Only based on clinical symptoms	12	9	21
EEG examination	26	18	44
Overnight EEG monitoring	8	9	17
Magnetoencephalogram (MEG)	5	3	8
Auditory tests			
Pure-tone audiometry	20	12	32
Speech audiometry	8	8	16
Other audiometry tests	0	1	1
Cognition test of environmental sounds	4	5	9
Source localization	1	1	2
Other tests related to hearing	1	1	2
Verbal function tests			
Peabody Picture Vocabulary Test (PPVT)	2	1	3
Illinois Test of Psycholinguistic Abilities (ITPA)	8	8	16
Standard Language Test of Aphasia (SLTA)	4	1	5
Others			
WISC-III	2	1	3
Kyoto Scale of Psychological Development	1	0	1
Tanaka-Binet Intelligence Scale	1	0	1
Auditory brainstem response (ABR)	19	17	36
Otoacoustic emission	0	0	0
Middle-latency response (MLR)	1	4	5
Slow vertex response (SVR)	0	0	0
Others	0	0	0
Event-related potential (ERP)			
Mismatch negativity (MMN)	0	0	0
P300	0	1	1
Others	1	0	1
CT	12	17	29
MRI	22	15	37
fMRI	1	4	5
SPECT	6	10	16
PET	5	5	10
Near-infrared spectroscopy (NIRS)	0	0	0
Others	0	2	2
Previously diagnosed at other hospitals	2	1	3

these patients. However, regarding audiometry, only about one-half of the reported patients were evaluated as to their pure tone receptive levels (frequency specific HLs) and word discrimination ability was only rarely determined.

3.1.1.1 Auditory Verbal and Language Symptoms

Auditory verbal symptoms are the most obvious signs of LKS. Although a small percentage of the patients showed delayed speech to some extent before the onset of their disease, they were usually able to pass the developmental milestones of one-word sentences, two-word sentences, and they had ordinary conversation skills. As gleaned from the previous reports, some patients seemed to be more intelligent than those encountered in the general population.

Some of the patients lost the ability to discriminate between almost all environmental sounds although they occasionally responded behaviorally to voices or sounds. The lack of the startle response to any sounds was also reported which may suggest the presence of cortical deafness in some cases of LKS (Hirano 1973; Tanaka et al. 1991; Kaga et al. 2004).

In some patients, only the fluency of their speech becomes impaired. Baby-talk-like speech becomes prominent and eventually it becomes difficult to understand what these patients saying. Grammatical errors and telegraphic style of writing are commonly observed. In the Japanese language, patients often abbreviate postpositional particles such as "ha, ga, wo, no", contract sounds such as "To*kyo*, Nin*ja*" and double consonants, such as "Ho*kka*ido, Sa*ppo*ro", are difficult to distinguish in the speech of these patients. Their intonation becomes strange and sounds like a different language. Inappropriate use of words, replacement of sounds, and various levels of difficulties in word recall are occasionally accompanied by roars, probably an expression of their emotional frustration at not being able to express themselves.

At the severest stage of the disease patients become mute and cannot understand what is spoken to them. Total aphasia becomes manifest and is profound in the advanced stages of LKS.

Basically, fluency in aphasia in childhood LKS is rare compared to adults with aphasia caused by cerebral bleeding or infarction. However, Suzuki's patient presented with fluent aphasia at the earliest stage of her disease, with extreme jargon (Suzuki and Takeuchi 1971). On the other hand, motor aphasia has also been reported. Some LKS patients have been diagnosed with motor aphasia only because they understood verbal commands.

In some cases of auditory agnosia and pure word deafness, patients can read and write letters and communicate with others by these means. Those patients made some errors in writing presumably caused by mishearing or distorted hearing even they could understand what they were told (Figs. 3.1, 3.2, 3.3, and 3.4) (see the case histories of G, H). Among the patients reported to have motor aphasia in the previously reported articles, there might have been patients who were on the recovery phase from sensory aphasia. In the recovery phase, patients often utter meaningless verbiage or say nothing at all. This particular speech abnormality is often seen in patients with aphasia caused by an organic brain lesion.

In the Japanese style of writing, four distinct types of characters are used (Fig. 3.5). Kanji are complex characters imported from Chinese characters around the third century AD. Each of these Kanji characters expresses an unique idea, a definite place or scene, or a sensation. In order to read a newspaper, a Japanese (Nihonjin) reader must be able to read approximately 2500 individual Kanji characters. Another character alphabet is Hiragana. In this phonetic alphabet, each Japanese vowel (a, i, u, e, o) has a unique simpler character, relative to Kanji, and each character can be read alone or in combination with one of the consonants (i.e., ka, ki, ku, ke, ko). Hiragana is used to modify a Kanji or to provide a phonetic reading of it. Forty-six Hiragana characters are in use. Katakana characters, of which there are also forty-six, are derived from a single stroke within a Kanji character and are of a slightly different form. Katakana characters are most often used to phonetically write a foreign (non-Japanese) proper noun such as a persons' name or a country name. Hiragana and Katakana were devised during the Heian era (794–1185 AD). Again, Hiragana and Katakana were both derived from strokes within the Kanji characters.

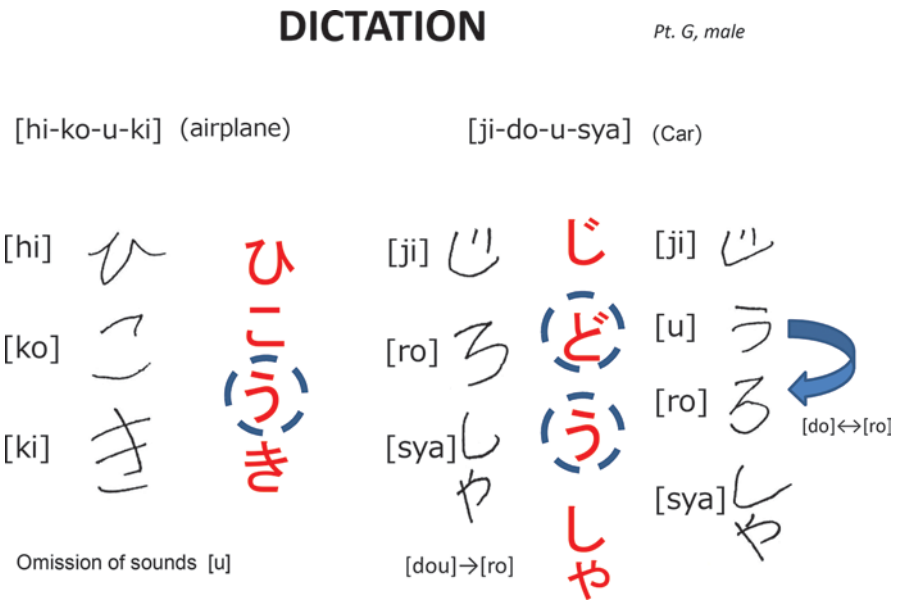


Fig. 3.1 Error in writing words by dictation. Patient G, 8 years old. Error in listening sounds is suspected

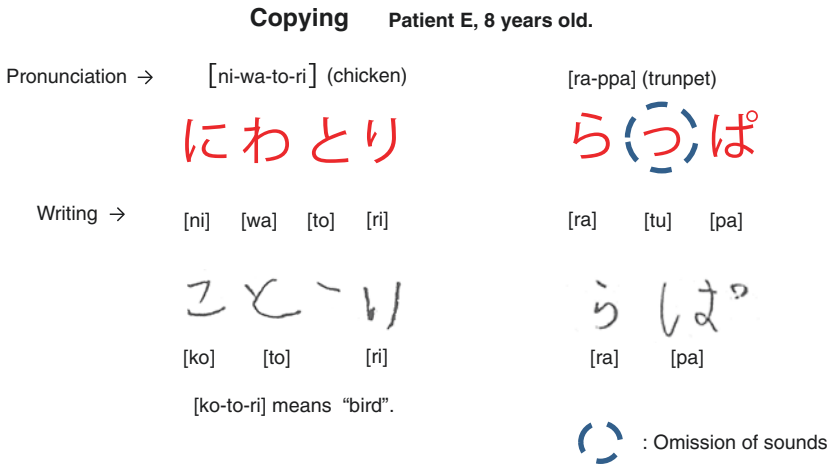


Fig. 3.2 Error in copying. Patient E, 8 years old. Words are shown to the patient and the patent was encouraged to write as the same. Error in special use of Hiragana (rappa → rapa) and analogous word of the same category (bird species) which is often seen in aphasic patient in the recovery phase

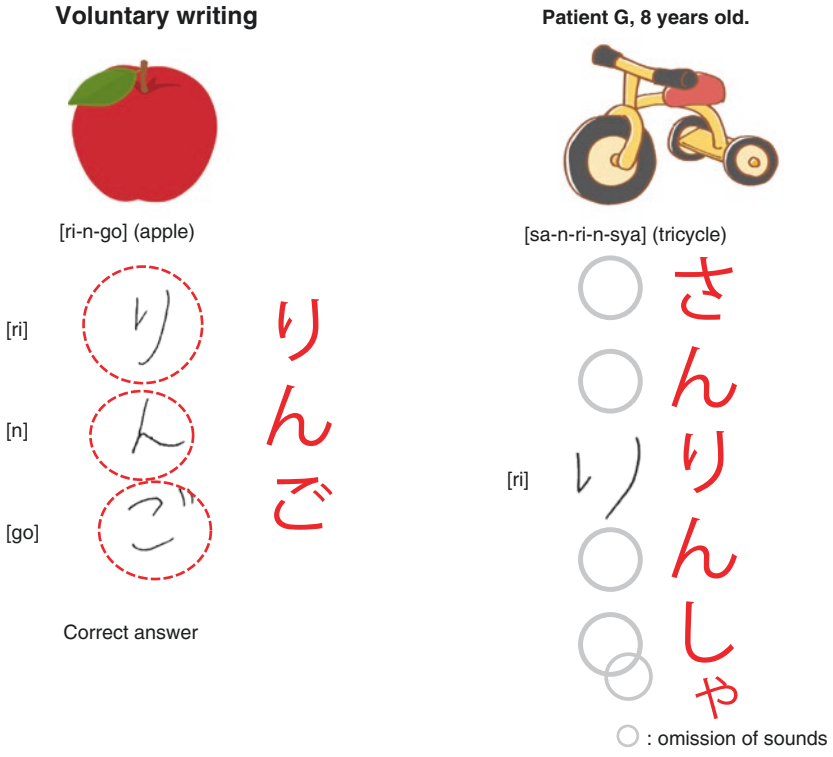


Fig. 3.3 Error in voluntary writing. Patient G, 8 years old. Pictures are shown to the patient and encouraged to write the name of the figure

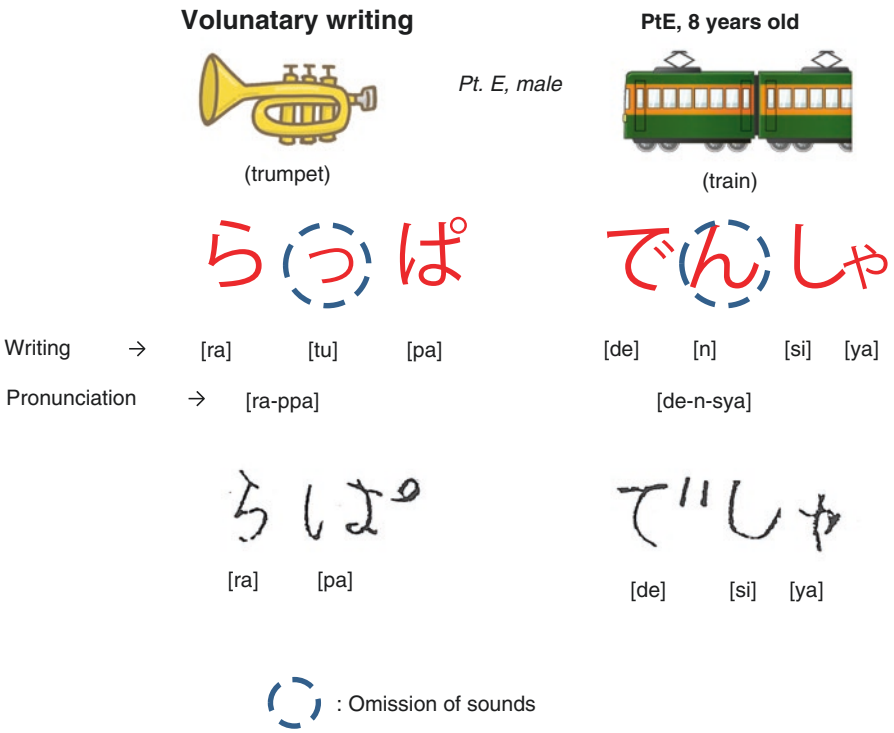


Fig. 3.4 Error in voluntary writing. Patient E, 8 years old. Pictures are shown to the patient and encouraged to write the name of the figure. Omission of the special use Hiragana

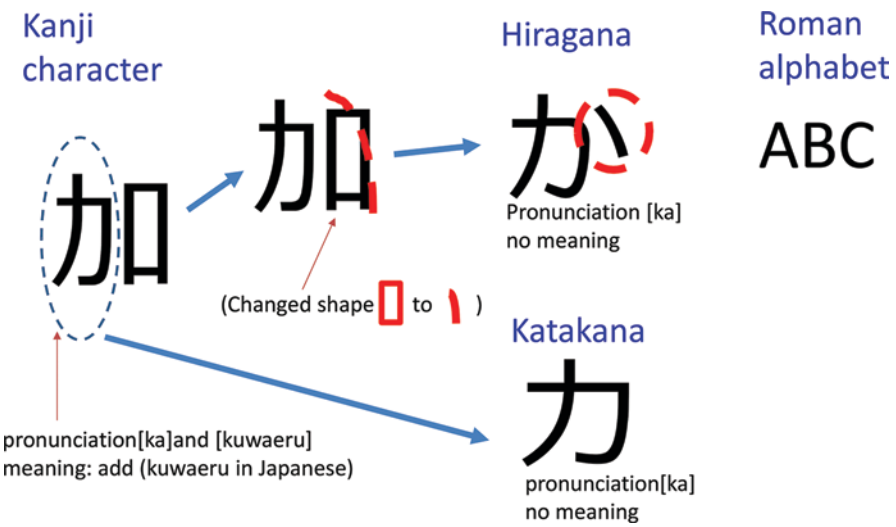


Fig. 3.5 How hiragana and katakana (Japanese phonetic letters) were made from Chinese characters in Heian areas in about tenth century. Refer the column

The original report in 1957 by Landau and Kleffner presents a very reasonable classification of LKS as aphasia and that total aphasia, at the severest stage of LKS, was often encountered among their patients. Historically, LKS had been reported as aphasia, auditory agnosia, or pure word deafness. A sensory component was often dominant in their aphasia patients. From the standpoint of internal language, most patients were free of disabilities and they were diagnosed with auditory agnosia or pure word deafness at some stage during their disease progress. Thus, Kaga first proposed that there was a hierarchical disability of language during the progress of the entire course of LKS (Kaga 1999). Her suggestion of hierarchy in verbal and nonverbal sound recognition is an interesting interpretation of the mechanism of this disease.

Language symptoms vary from time to time relative to the stage of the disease. One of our patients exhibited definitively different clinical features during their disease progress such as total aphasia, sensory aphasia, verbal and nonverbal auditory agnosia, verbal agnosia, and word deafness. The disease progressed but the patient later recovered. Thus, in our patients, the clinical features of LKS differed during each stage of their disease progression. In addition, exacerbations and remissions are occasionally observed and the severity of the disease often differs from time to time. This may explain why many physicians have assigned different names to this disease. This suggests that these different names are dependent upon the stage of the disease when these physicians first encountered their patients. This finding causes us to speculate that the severity of LKS and its underlying lesions as revealed by EEG differ relative to the stage of the disease. One patient, who recovered completely, said that he could hear music and noises with no differences during his impairment whereas his reception of speech sounds was unusual (patient E). Another patient said that he understood what he was told but that he was not able to speak a word (patient G). This latter patient may have had a type of motor aphasia. Another patient reported that he could understand what he was told but that could not put together the words to appropriately respond.

From these original publications, I speculate that those patients were aphasic, especially as to the sensory components of speech, which began at an early stage of their disease and which, during lengthy follow-ups, continued to be the most prominent symptom over the long term and most of these patients were free of disabilities in their internal language. These symptoms probably caused agnosia to be emphasized in LKS patients. The rarity of this disease, especially during early diagnosis, is often quite difficult. One reason for the variety in the nomenclature of LKS can be attributed to the above findings.

One of our patients presented with unique clinical features during each stage of the disease progress, i.e., total aphasia, sensory aphasia, verbal and nonverbal auditory agnosia, verbal agnosia, and word deafness. Further episodes of exacerbation and remission were occasionally observed over the 2–3-year course of the disease and the severity of the disease often fluctuated. This is another reason to name the dysfunction of LKS based on its verbal symptoms. The above physicians including me encountered their patients at various stages of their disease progress resulting in the variety of reported nomenclatures.

As pointed out, LKS language symptoms vary from stage to stage during the disease progress. It is thus reasonable to presume that the recognition of verbal and nonverbal sounds in this disorder are stratified or disposed in layers chronologically (Kaga 1999). The evolution and transitions of these clinical features are very important observational elements in the classification of the underlying mechanisms (etiology) of LKS.

LKS patients display unique symptoms during each stage of their disease progress and, on this basis, there is a tendency toward misdiagnoses of these patients especially during the early stages of their disease. We emphasize that caregivers should pay close attention to auditory verbal and language symptoms and to ensure good communication with their patients. If a patient has verbal auditory agnosia and he/she can write letters, communication with others may only be attained by writing letters to each other.

The symptoms of LKS differ relative to its current severity, its stage, and to the individual characteristics of the disease. During recovery phases, patients often show a form of disarticulation which is often seen in patients with aphasia caused by an organic brain lesion.

3.1.1.2 Musical Abilities

Research in the study of brain functioning cannot evolve without adequate and accurate clinical case reports, this even in this age of spectacular advances in functional brain imaging techniques.

Amusia is a disturbance in the perception of music caused by acquired brain lesions. Disturbances in the musical perception of music are usually classified into a sensory type or a motor type which are consistent with classical sensory and motor aphasia. Historically, amusia has been observed in professional or high-level amateur musicians (Botez and Wertheim 1959; Wertheim and Botez 1961) resulting in an apparent decline in musical ability occurring both before and after the onset of LKS.

Disturbances in the perception of music can be further classified as those involving poor discernment of melody or those involving the disturbed perception of rhythm or time intervals. In this section, we discuss the various types of amusia noted above, specifically abnormalities effecting the perception and performance of melodic music and amusia which effects the perception of rhythms, pitches, and timbre.

Patients with amusia present subjective (emotional) disturbances which manifest quite differently relative to those disturbances effecting their technical (motor) ability regardless of the patients' experience with or affinity for music. Cerebral lesions underlying general agnosia are usually confined to bilateral lesions in the temporal area of the auditory cortex or to their bilateral auditory radiations. The area of cortical involvement underlying amusia is thought to be slightly more widespread than that seen in patients with general auditory agnosia. On the other hand, patients with amusia, who are relatively naïve in musical appreciation or performance, seem to

show quite different cerebral abnormalities (Bever and Chiarello 1974; Shanon 1980). Positron emission tomography, or PET scans, initially reported by Mazziotta et al. (1982) indicated that disturbances in the perception of melodies, timber, rhythm, and pitch were related to pathology of the left inferior frontal lobe, the superior temporal gyrus, or the right inferior frontal lobe. Pathological changes in Broca's area and in the left cuneus or frontal cuneus of the occipital lobe have also been implicated (Platel et al. 1997).

Disturbances in the perception of *melody* have been reported to arise from pathology in the right hemisphere. However, disturbances in the perception of *rhythm* have been shown to arise from pathology effecting a wide range of cerebral structures, i.e., the left hemisphere, the basal nuclei, the cerebellum, and various subcortical systems (Russel and Golfinos 2003).

In studies of patients who underwent a temporal lobectomy, musical ability was disturbed in patients who had a right hemispherectomy but no changes in musical ability were noted in patients who had a left hemispherectomy (Shankweiler 1966; Zatorre 1985). Zatorre noted that if the transverse temporal gyrus was resection on either side then this resulted in disturbed musical ability.

Clinically, four adult patients with auditory agnosia were evaluated in terms of their understanding and perception of the various components of music (Shindo 1996). The authors indicated that loudness and time intervals could be discerned separately in their patients if these differences were clear enough. However, these patients almost completely lost their ability to discern pitch and timbre. Their cerebral lesions were found to be in the bilateral temporal lobes, either in the auditory cortex or its radiations. These findings are identical to or part of the findings in auditory agnosia.

Amusia is often a symptom in patients with LKS. Pötzl, in 1926, attempted to delineate the differences between amusia and aphasia. However, until Kaga's article, amusia was almost hardly mentioned in the literature. Kaga described about four patients who lost their ability of musical perception. One boy, aged 6 years (patient C), showed amusia as a compliment of his symptom of auditory agnosia of environmental sound. Another boy, aged 6 years (patient E), who had typical auditory verbal symptoms began to play piano but out of tempo, rhythm, and harmony which, previously, he could play very well. His symptoms continued for 10–14 days and then gradually subsided. After he became an adult of 30 years he became a businessman and he said he played the piano very skillfully in spite of his clinical symptoms typical of LKS during childhood. I have not confirmed his present ability in playing the piano. In another patient (patient G), his musical ability as a 5-year-old vocalist before the onset of his LKS was excellent but, following the onset of LKS, he became disinterested in singing and, during the acute stage of his LKS, he became indifferent to any music whatsoever. Patient D, who has been followed up for 50 years, was a cheerful girl of 4 years of age, spoke much, and sang many songs. However, she incurred auditory agnosia at the preschool age 4 at the latest and she has suffered from severe residual symptoms since then. She lost her ability to sing on key and she lost her sense of rhythm. She cannot differentiate between the timber of various instruments and she cannot distinguish the rhythms or remember

the melodies of formerly favorite nursery rhymes. Her singing has become like that of a monotonous reading of a sutra with no melody line, out of tempo, and no defined rhythm. This patient, patient D, formerly enjoyed singing as a toddler. But after she incurred LKS at 4 years of age she has never been able to sing acceptably. Her singing is completely out of tempo and without melody. Because she is so sincere about participating in Karaoke with her friends, she has taken singing lessons to improve her ability to sing well once again.

In light of these patients' symptoms and experiences, I now always inquire of the parents of these children as to their child's previous or current musical abilities. Since I have started these parent inquires I have not encountered a single LKS patient with previous or current intact musical ability. For example, patient B, female age 4, loved and sang songs accompanied by animation before her disease onset; however, after her onset of LKS, her singing was not melodious and was lacking in tempo and rhythm. She is now 10 years old but her singing is still impaired.

Deonna T became interested in amusia in his LKS patients. He devoted a special section in his book to amusia in LKS. In a personal communication with me, he introduced my comments related to the level of education in music in Japan and to amusia in LKS patients (Deonna 2016).

In Japanese, music education is a compulsory subject from elementary school through junior high school. Even before entering elementary school, children are exposed to many opportunities to sing various songs during nursery school and kindergarten. Many of these children often matriculate to commercial music schools to learn how to play the piano, organ, or other some musical instrument. Therefore, children who are not adept at music are often easy to detect. Karaoke was invented in Japan and has since been exported worldwide. Still, people with LKS who are musically challenged are sometimes embarrassed with their performance in this genre.

3.1.2 LKS Patients' Subjective Awareness of Their Own Disease

Among LKS patients, the subjective awareness of their disease varies with the stage of their disease. At its severest stage, patients are not aware of the severity of their disease nor with their auditory difficulties in comprehending words or environmental sounds. This phenomenon is thought to be due to agnosia of their disease and is classified as anosognosia. Anosognosia is a denial of the patient's apparent physical or sensory dysfunction. This may be attributed to an abnormal body image or to loss of sensory integration due mainly to pathology in the right parietal lobe or to a disconnection to the diencephalic/limbic system over a wide area. Anosognosia in LKS patients may share common pathology with those of acute aphasic patients. Anosognosia in aphasia was first precisely described by Alajouanine in 1956.

Anosognosia necessarily involves a patient's inability to recognize their own disability and thus, anosognosia of language is thought to include some components of sensory aphasia or auditory agnosia.

During the recovery phase of LKS some patients begin to express their concerns relating to their condition. One patient's family reported that their child asked, "Why can't I hear?" upon first attending a school for the hearing impaired. Another patient, a junior high school student became depressed because of his inability to recognize speech and understand the conversation.

Some patients who wished to be understood by others became hyperactive or even aggressive. Some of these behavioral disorders could have understandably arisen secondarily to their communication difficulties. But usually, behavior dysfunctions seem to be the primary phenomenon than to be the secondary symptom from the clinical observation.

3.1.3 Behavioral Dysfunctions

Hyperactivity, inattention, and flamboyant behaviors are observed in some patients with LKS and this often leads to an incorrect diagnosis of attention-deficit hyperactivity disorder (ADHD). However, ADHD is a "congenital" developmental disorder and it is never expressed after children have developed to adulthood. In some cases, these changes in behaviors and emotions were so profound that persons involved in the care of these patients found it difficult to understand their abnormal psychological propensities. Consequently, parents and even physicians often suspected that such patients suffered from psychiatric disorders.

Bishop determined that 19.4% (24/124) of his LKS patients had behavior disorders (Bishop 1985). Beaumanoir reported that 71.4% (68/95) of his patients exhibited behavior disorders and 80% were hyperactive (Beaumanoir 1985).

In our Project B survey of 60 patients, emotional changes prior to or following seizures were present in 74.1% (43/58) of our cases and absent in 25.8% (15/58). The symptoms of behavioral changes which were seen in our patients were hyperactivity in 28, aggressive behavior in 17, and depression in 4. A strange lightheartedness was observed in 1 patient. Moreover, 34 patients had multiple behavioral abnormalities such as hyperactivity, poor attention span, temper tantrums, selfishness, rudeness, and lachrymation (Table 3.6).

3.1.4 Family History

The family histories of LKS are usually negative. However, some cases of LKS with familial histories were discovered. In the first report of LKS (1957), Case 2 was the elder brother of Case 1. Both of them had a seizure disorder with aphasic symptoms.

Table 3.6 Emotional behavior before and after the onset of LKS (Project B)

	Male	Female	Total
Observed changes	25	18	43
Hyperactive	18	10	28
Aggressive	11	6	17
Strange vivacity	1	0	1
Gloomy	2	2	4
No changes	10	5	15

However, their other cases, four girls, had no family histories of convulsive or communication disorders.

Rapin I published her findings of a set of male siblings with verbal auditory agnosia. Case 5 was a younger brother of Case 4. However, she indicated that case 5 had not only had no seizures but also had a normal EEG despite his brother showing similar symptoms (Case 4) (Rapin et al. 1977). Thus, this patient (Case 5) may not have had LKS.

In publications within Japan, Nakano presented a pair of siblings with LKS. The elder sister developed aphasia at age 5 and convulsions 1 year after the aphasic episode. Her younger brother developed convulsions with several neurological symptoms including ataxia, hemiparesis, urinary incontinence at his age of 4 years and 10 months. One year later this younger brother developed aphasia. Both siblings underwent spectral topographic mapping by EEG and the authors concluded that electrophysiological dysfunction in the fronto-centro-parietal areas was associated with markedly unstable and paroxysmal discharges and these findings were the main feature of Landau–Kleffner syndrome (Nakano et al. 1989).

At least three sets of siblings have been reported in the literature to have had a family history of LKS. Most families who were not mentioned about the epilepsy or LKS might not have problems in their family history. Genetic studies were not obtained in these three sets of siblings in that this technology was not available at that time.

I have examined the EEGs of the parents of two patients who did not have a history of LKS nor a questionably related disease. No abnormal EEG findings were discerned in these parents.

It seems that a positive familial history of LKS is incidental at this point and that LKS itself is unlikely to be heritable.

3.1.5 Physical and Neuropsychological Examinations

Physical and general neurological examinations are usually normal in LKS patients. Other than auditory agnosia, all other types of agnosia are usually not observed in LKS. However, precise neuropsychological examinations occasionally reveal that LKS patients manifest apraxia of dressing or a construction apraxia. These symptoms may be due to the change of mental state caused by subclinical epilepsy but it

is necessary to observe each patients' behavior carefully. Patient C could write "kushi (comb in Japanese)" seeing the picture of a comb but he could not know how to use it when he was 7 years old. By EEG, no organic anatomical brain lesions were seen, including within the parietal lobes. During the acute stage of LKS, some patients demonstrate mild to severe clumsiness. These phenomena also may be related with subclinical epilepsy.

A very limited number of LKS patients (Nakano et al. 1989) incur one or more convulsions, ataxia, hemiparesis, and urinary incontinence. In one of our patients 4 years and 10 months of age, these pathologies may have been associated with an occult epileptic event. One year later he subsequently developed aphasia. The relationship of these events in this patient is difficult to comprehend. But if we consider that his verbal symptoms followed his epileptic episodes by a full year then we can only conclude that this patient had LKS.

3.1.6 Intellectual Ability or IQs (Intellectual Quotients) in LKS Patients

In general, patients with LKS have the normal intellectual ability. However, in some patients, their IQs varied, on successive tests, over time. These IQ changes seemed to be synchronized with the severity of their auditory verbal symptoms. Their performance IQs usually exceeded their verbal IQs due to their delayed acquisition of language ability. However, this variability in their scores persisted even after their apparent complete recovery of their language ability.

In fact, our seven patients whose IQs were determined on the Wechsler Intelligence scale often scored higher than 100 on both their performance and verbal IQs. One patient whose full IQ, verbal IQ, and performance IQ scored 68, 68, and 75 over subsequent tests and demonstrated a ratio of correct responses of 33/36 on the Raven's Colored Matrices test. This indicates that the patient had normal visual reasoning. Thus, this patient's intelligence was considered to be almost normal. Another patient could not have her IQ evaluated; however, her daily behavior and her responses to her environment suggest that she had an IQ of at least 80. Considering their handicap in understanding auditory verbal stimuli, the intelligence of LKS patients does not seem, on the whole, to be impaired. In the acute stage of the disease, it is often difficult to evaluate IQs and other abilities in these patients because these evaluations require their cooperation, which is often problematic. Worster-Drought, who published a second paper following by Landau and Kleffner's paper, found that his patients' intelligence scores (IQs) were higher than the average (Worster-Drought 1971).

Bishop reported that only 9 of his 124 patients (7.5%) scored under 80 on their nonverbal IQ test (Bishop 1985). This finding is almost identical to that from our study. In addition to the poor prognosis regarding the development of intelligence in LKS patients, Bishop pointed that there was a poorer prognosis for auditory verbal symptoms if they had their onset at a young age.

In our survey B of 60 Japanese LKS patients, 8.3% (5/60) of them applied and qualified for an intellectual disability certificate issued by the Japan social welfare system. This certificate is issued to persons whose IQs are less than 70 found prior to their age of 18 years and who have difficulty living at home, difficulty in school, and with socialization. Usually, because these patients have residual auditory verbal symptoms, they have difficulty in acquiring new knowledge by listening or by reading material. In other words, they have difficulty in learning.

Most LKS patients showed normal intelligence overall, but be that as it may, some patients scored on their intelligence tests at less than 80 on their performance IQs or occasionally on their overall IQs. Of course, an IQ score of 80 does not reflect their level of intellectual disability but it does affect their daily lives. This contradictory finding that patients had both good non-verbal IQ scores and poor verbal IQ scores was commonly observed. To further assess these LKS patients' non-verbal IQ scores, the Raven complex figure test is useful. Some patients could not be evaluated as such because of their disabilities in the acute stage as noted above.

These results lead to a more comprehensive understanding of the variations in the electroencephalographic prognosis of these patients with ESES or CSWS. Both of these cases had electroencephalographic findings as common clinical findings. LKS patients displayed ESES at an early stage of their disease. However, ESES and CSWS symptoms are often seen in patients with intellectual disabilities and long-term ESES often results in these patients' intellectual deterioration. ESES and CSWS have always been a controversial issue but the recent trend of thinking it is to think of them as being almost identical. because of the similarities of these electroencephalographical abnormalities, i.e., benign Rolandic epilepsy and extreme epileptic abnormalities such as noted in ESES and CSWS, the disease process itself has become classified as a spectrum disorder in that some patients had language disorders, like aphasia, accompanied by epileptic episodes. I am not sure whether it is appropriate to categorize LKS as a spectrum disorder in that these patients' symptoms are so unique as regards their auditory verbal symptoms in light of their intact intellectual capacities as a principal.

3.1.7 Epileptic Seizures

A classification of epilepsy has recently been proposed by the International League Against Epilepsy (ILAE). In 2017, this new classification of seizure types and epilepsies was announced and some changes in the wording of seizure types were recommended. These changes include partial seizure to focal seizure, simple partial seizure to focal aware seizure, complex partial seizure to focal impaired aware seizure, psychic seizure to cognitive seizure, and secondary generalized seizure to focal to bilateral seizure. Although the revised terminology is reasonable, at this point, these changes do not seem to be applicable regarding the traditional descriptions of seizures in LKS patients. As such, in this text, I use the original terminology and the traditional classification of seizures and epilepsies.

Clinical epileptic seizures in LKS patients have been classified by their various types, i.e., focal motor seizures, secondary generalized tonic–clonic seizures, myoclonic seizures, complex partial seizures, and "petit mal" seizures which have a lower incidence.

Beaumanoir (1985) reported that more than half of his patients with LKS presented with at least three types of epileptic seizures. The onset of these epileptic seizures began between 6 months and 13 years of age and the onset age-range of these seizures was narrower than the onset of auditory verbal symptoms. Seventeen to 25% of these reported patients did not experience clinical seizures (Deonna et al. 1977; Beaumanoir 1985).

Among the seizure types of LKS partial motor seizures are the most commonly observed. Some intractable seizures were observed and described in the recent literature (Downes et al. 2015). Electrical status epileptics during sleep (ESES) was described by Patry et al. (1971), and the EEG findings of LKS patients often fit the criteria of ESES. Of Patry's patients, five out of six had intellectual disabilities and he said two of his patients could not regain their language ability. Kellerman described the auditory verbal symptoms in his patients with ESES. However, some other authors have postulated that another criterion of EEG, continuous spikes, and wave complexes during slow sleep (CSWS) were similar to the seizure types observed in LKS patients. Epileptologists vary in their interpretations of ESES and CSWS. The relationship between LKS and ESES/CSWS is, therefore, complicated and controversial.

Our Project B survey revealed that the average age of onset of LKS was 5.2 years. Auditory verbal symptoms and epileptic seizures generally had independent onsets.

In some patients, epileptic episodes began between 1 month up to 8 years prior to the onset of their auditory verbal symptoms. In some other patients, their auditory verbal symptoms began between 2 months of age and up to 3 years of age prior to the onset of their seizures. Ten patients presented auditory verbal symptoms which began just after the onset of their seizures (Table 3.7).

Beaumanoir reported that in 45.5% of his cases (68 patients) auditory verbal symptoms were observed prior to their epileptic seizures (Beaumanoir 1985). In 16.1% up to 17.6% of his patients, whose first symptom was an epileptic seizure, verbal and epileptic seizures occurred almost coincidentally (Table 3.8).

The frequency of seizures among LKS patients varies. Some patients have only a single seizure whereas others may have frequent seizures or seizure clusters. Twenty-five percent of Beaumanoir's patients had no seizures whatsoever. Status epilepticus was observed at least in two of his patients (Beaumanoir 1985). Overall, epileptic seizures are effectively controlled with medication. Most medicated patients show a marked reduction in the frequency and severity of their seizures and they often become seizure-free. In very rare cases, their seizures are medically intractable and these patients often undergo temporal lobe resections (Cross and Neville 2009).

Our B survey of 60 LKS patients divulged that 52 of these patients incurred clinical epileptic seizures and four had no seizures. No mention of seizures was made in four of these patients and it is probable that they, in fact, actually had no seizures.

Table 3.7 Epileptic seizures symptomatology of Project B

	Male	Female	Total
Epileptic seizures			
Present	33	19	52
Not present	1	3	4
Seizures described			
Simple partial seizure	8	5	13
Complex partial seizure	8	7	15
Atypical absence	2	1	3
Absence seizure	5	1	6
Astatic	1	0	1
Atonic seizure	1	2	3
Generalized tonic–clonic seizure	10	1	11
Secondary generalized tonic–clonic seizure	4	1	5
Focal seizure	1	1	2
Focal motor seizure	1	1	2
Eyelid myoclonia	0	1	1
Lennox–Gastaut syndrome	2	0	2
Seizure frequency			
Daily	2	1	3
Once in a couple of days	3	1	4
Weekly	2	0	2
Monthly	7	6	13
Several times a year	9	4	13
Yearly	0	0	0
Once in a few years	2	2	4
Less than above	3	1	4

These survey percentages of seizure incidence in LKS patients seem to be a little low and may reflect the various clinical emphases of the specialty of the respondents. Not all of the patients described in the survey had clinical seizures despite presenting grossly abnormal EEG findings. The survey respondents' descriptions of seizure types were quite variable. However, the survey data indicated that the occurrence of partial seizures, either simple or complex, was definitely dominant in these patients and many types of seizures were described.

3.2 Electroencephalography (EEG)

Marked abnormalities in the EEG in acute phase of the disease are the hallmark of LKS. Examples of the EEGs are shown in this section. Figures 3.6 and 3.7 are the examples of the EEGs of a patient (patient A in Sect. 6.1 in her acute phase).

Table 3.8 Epileptic seizures symptomatology (Beaumanoir 1985)

	n	%
Frequent seizures (39 cases)		
Several types of seizures	17	43.5
Seizures described		
Grand mal	9	
Benign epilepsy with Rolandic spikes	14	
Hemiconvulsion	5	
Partial complex seizure	3	
Absence (petit mal)	4	
Astatic seizure	5	
Convulsive (not identified)	3	
Jacksonian seizure	1	
Rare seizures (19 cases)		
Generalized tonic–clonic seizures	3	
Benign epilepsy with Rolandic spikes	6	
Hemiconvulsion	2	
Partial complex seizure	1	
Absence seizure	4	
Astatic seizure	2	
Convulsive (not identified)	5	
Single seizure (7 cases)		
Generalized tonic–clonic seizures	2	
Benign epilepsy with Rolandic spikes	1	
Hemiconvulsion	1	
Partial complex seizure	1	
Convulsive (not identified)	2	
Unique episode of status epilepticus (7 cases)		
Status epilepticus during follow-up (3 cases)		

If a patient with LKS is suspected of having something amiss or something unusual to them in auditory verbal symptoms at the early stage of their disease, their EEG definitely is abnormal even if they had incurred no clinical epileptic seizures. It is also surprising that patients with LKS with remarkable EEG abnormalities at first, finally their EEGs usually turn out to be normal or almost normal after several years of their onset of the disease. Characteristic findings in the EEG traces of epileptics usually are frequent spikes or spike and waves.

Spikes, spike and waves, sharp and slow-waves are frequent manifestations of the EEG findings in patients with LKS and their occurrence is a function of each patients' disease stage. Paroxysmal abnormal focal EEG tracings can be detected over any cortical area and they may or may not be symmetric. A number of clinicians have postulated that there is a left temporal predominance of cortical

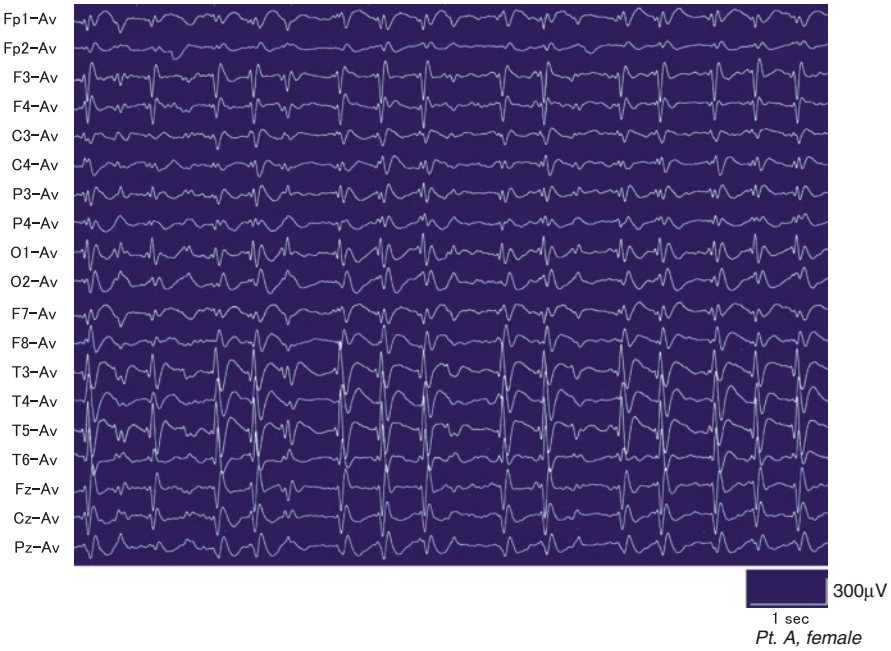


Fig. 3.6 Sleep EEG record of patient A in an acute stage, 4 years old, female. Her auditory verbal symptoms of LKS were evident. She also had several times attacks of loss of consciousness in a day despite enough VPA. Bilateral mid-temporal high voltage 1.5–3 cps spike-wave complex was seen

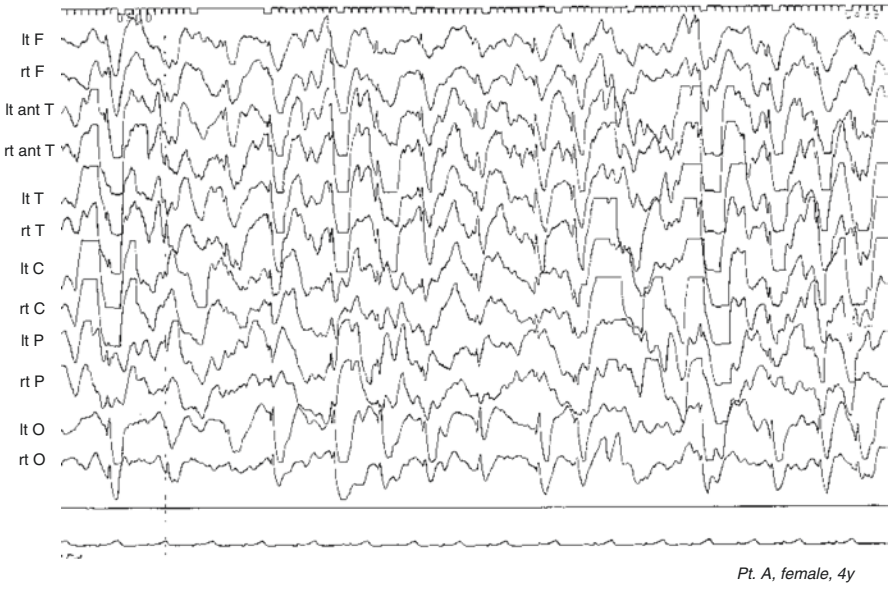


Fig. 3.7 Sleep EEG record of patient A, 4 years old. Left temporal dominant spikes can be detected

pathology in LKS patients (patient E) (Figs. 3.8 and 3.9) but this seems not to be always the case. In some patients, a right temporal preponderance of pathology is apparent (patient I) (Fig. 3.10) and a few other patients exhibit a central or parietal dominance on either cerebral side. Multifocal EEG cerebral discharges have been seen to occur. Unilateral or bilateral EEG activity can be recorded and EEG abnormalities in LKS patients decrease with their age. Interestingly, patients with LKS may show a full recovery from their EEG abnormalities (i.e., patient D) (Fig. 3.11) even after a sequela of their verbal and hearing problems (Mascetti et al. 2009). Their patients' background EEG activity was usually normal but demonstrated some slow-wave activity.

Spike focus is often located in the left side and the right side focus is also present.

Some of the patients (like patient H in Sect. 6.8) show independent bilateral foci in their EEG (Figs. 3.12 and 3.13).

It appears obvious that abnormal EEGs during sleep are much more common than in awake LKS patients, at least during the early stage of their disease. This phenomenon was noted by Landau and Kleffner in their earlier study. The discovery of and the technique of recording cerebral neural activity, EEGs, was first published

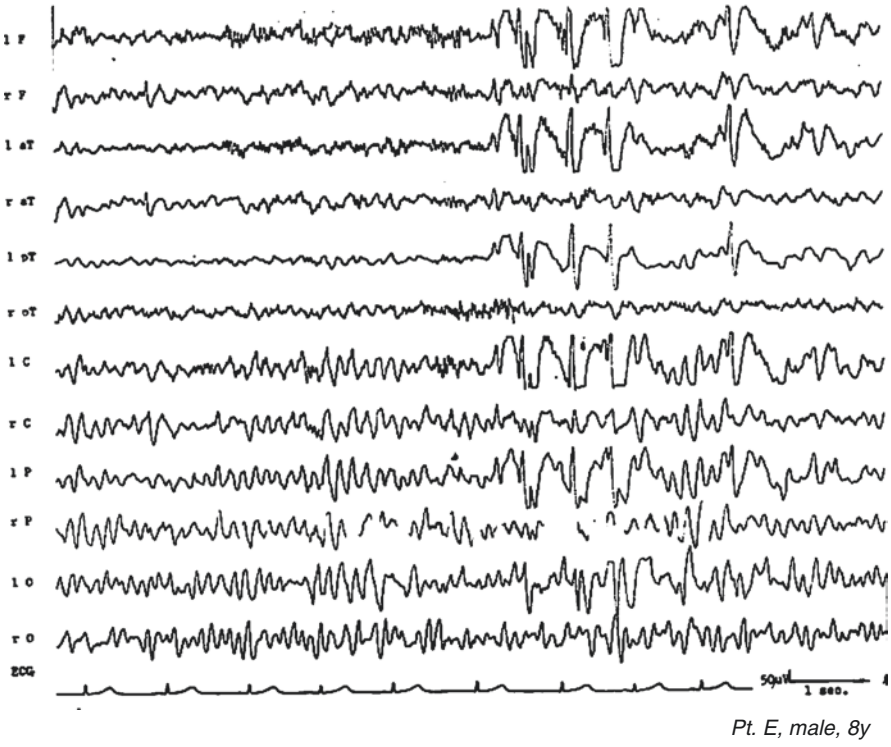


Fig. 3.8 EEG of patient E. 8 years old, male. Awake record. Eight to 9 cpc alpha basic activity with some theta waves is seen as a basic activity. Paroxysmal left temporal dominant spikes are present frequently

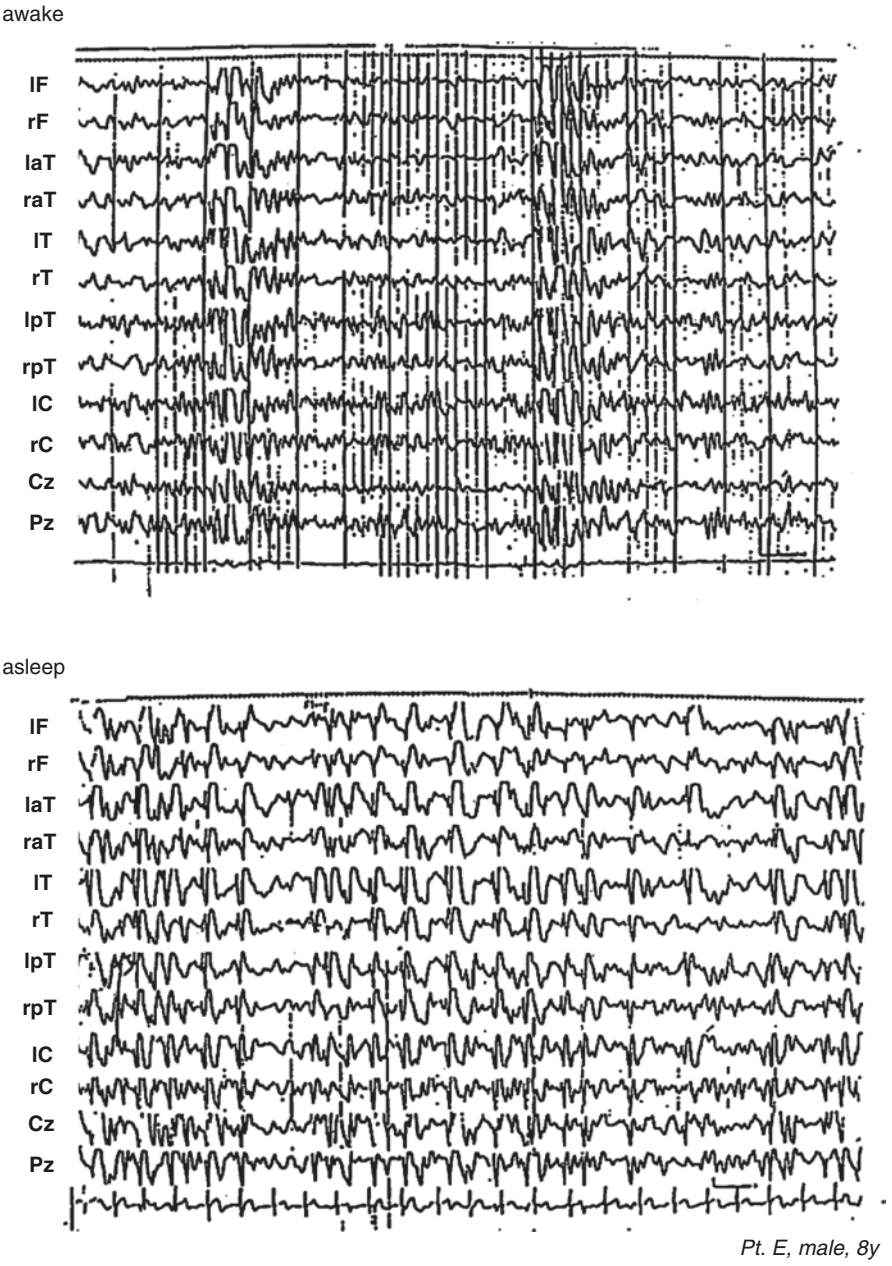


Fig. 3.9 EEG of patient G, 8 years old, male (Kaga et al. 1999). Difference of EEG abnormalities in a patient. The upper case is an awake a sleep record. The lower case is asleep record. Paroxysmal activity increased during asleep record

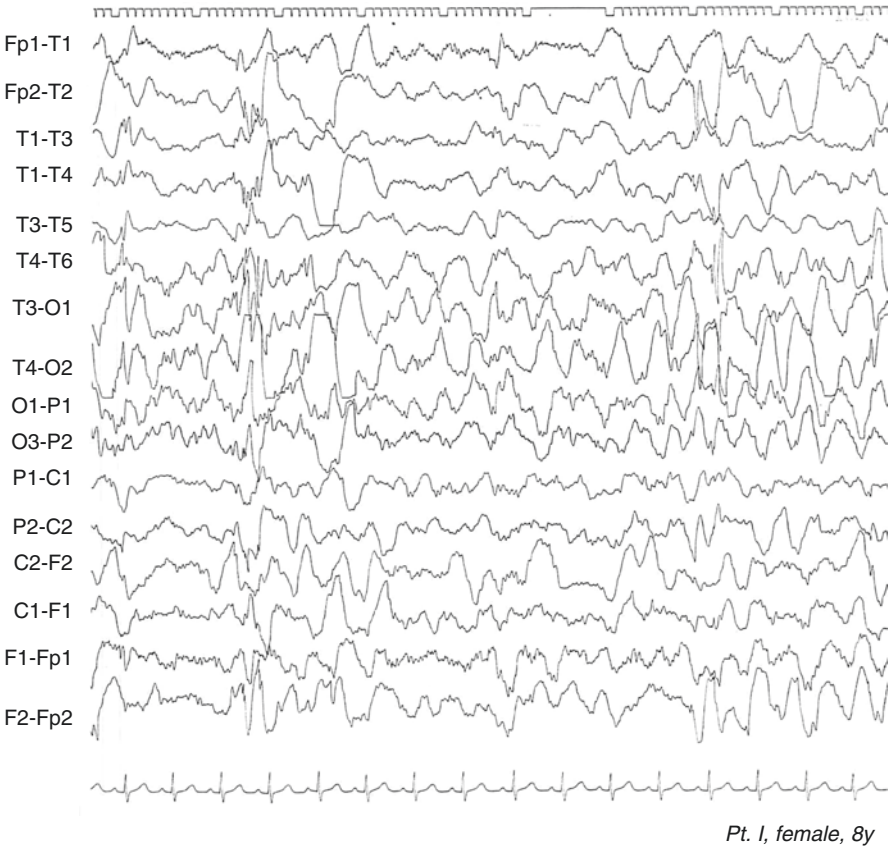


Fig. 3.10 EEG of patient I, 8 years old, female. Right dominant paroxysmal activity is present

in 1929 by Hans Berger. Thus, Pötzl, in his 1926 study, made no mention of EEGs as this technique had not been developed at that time. Since its development, the acquisition of EEG activity has become an interesting and necessary tool for clinicians involved in the care of LKS patients. Kellermann, in 1978, was the first clinician to describe the relationship between LKS and electrical status epilepticus during sleep (ESES). ESES is an EEG pattern which can be described as the appearance of continuous spikes and waves during the deep sleep stage, namely, during the slow-wave sleep stage (stage IV). Tassinari (with Kellermann in 1978) noted that the typical pattern of ESES was often recorded in more than 85% of the recording time taken during their patients' sleep and this pattern was dominated by spikes and waves. Tassinari, and others, have noted short-term memory deficits and language impairment, lowered IQ, hyperkinesia, and even aphasia in patients who presented the typical ESES pattern (Tassinari et al. 2000).

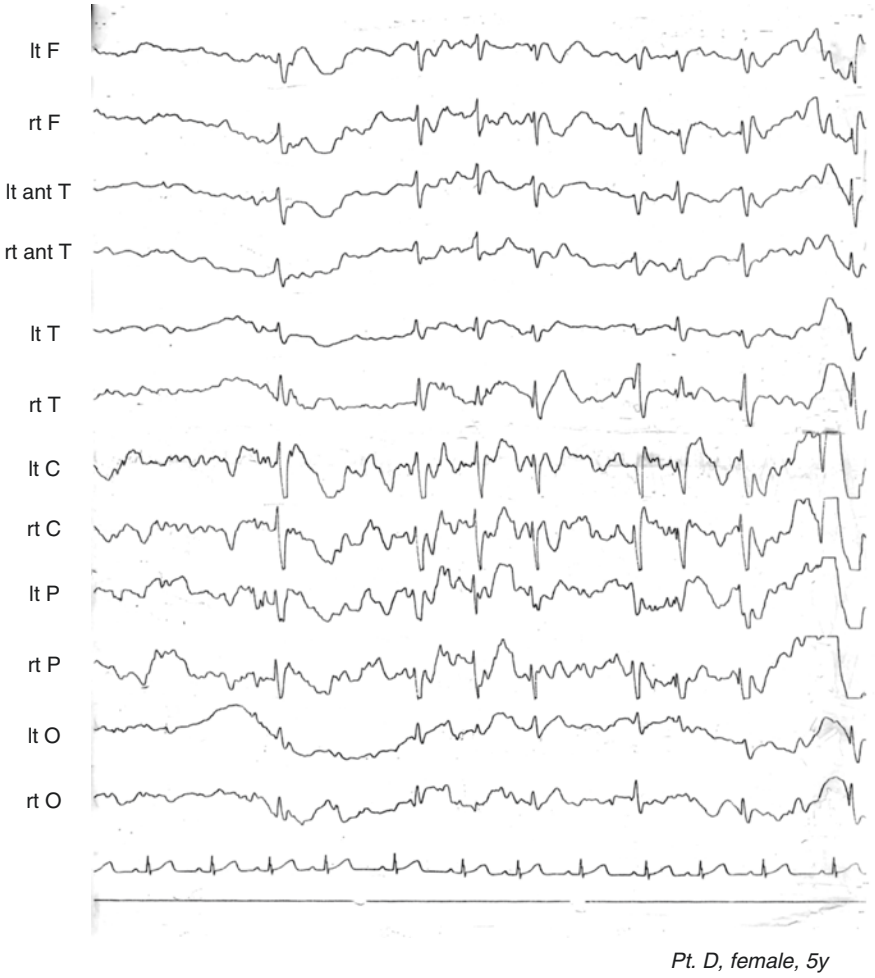


Fig. 3.11 EEG of patient D, 5 years old, female

Thus, the determination of ESES has become a necessary electroencephalographic clinical criterion to resolve the presence of paroxysmal epileptic discharges. ESES is seldom seen in patients with ordinary acquired aphasia of organic brain lesions. LKS is often concurrent with ESES therefore, ESES does not uniquely define the LKS patient. It is noteworthy that EEG tracings in LKS patients change very quickly. The percentage of paroxysmal spikes and waves is variable and not always the same. On the other hand, an active controversy between the distinction between ESES and CSWS (continuous spike-wave activity during slow

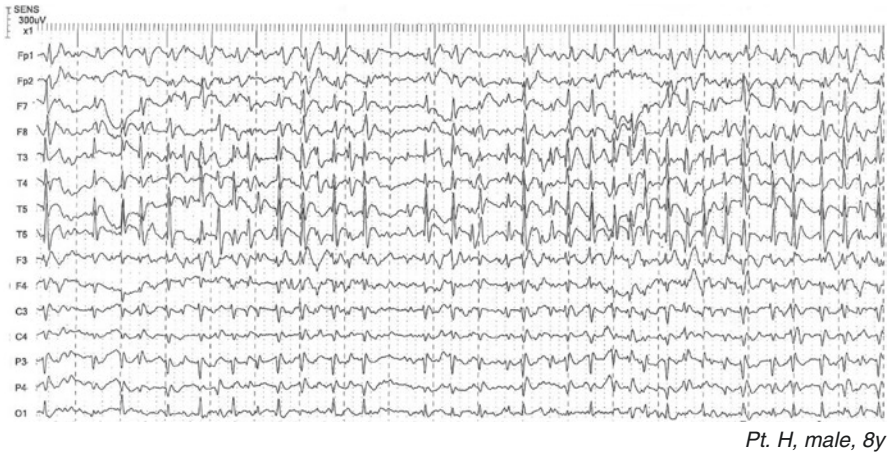


Fig. 3.12 EEG of patient H, 8 years old, male. Left mid to posterior temporal spikes are frequent. Sleep record

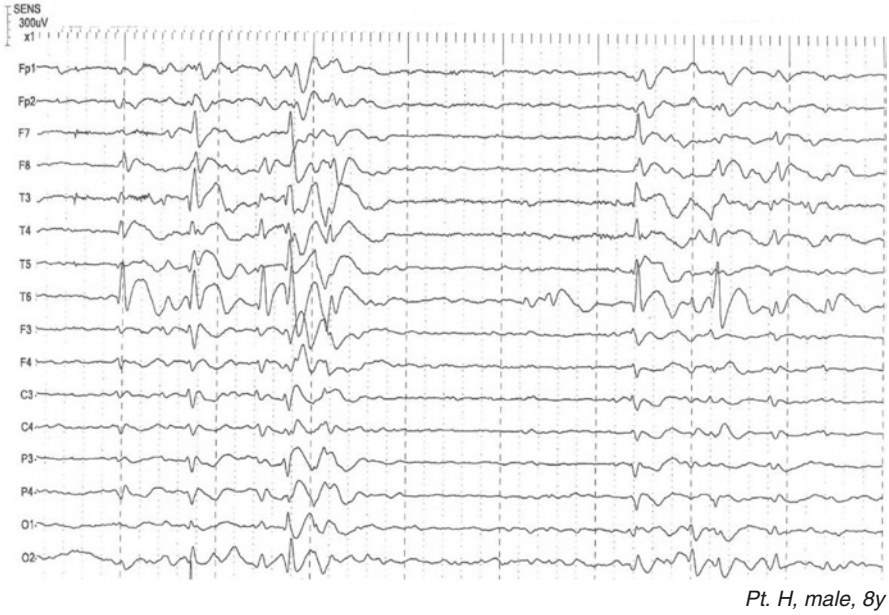


Fig. 3.13 EEG of patient H, 8 years old, male. Left and right temporal spike activities can be detected

sleep) is on-going (Party G, Lyagoubi S, Tassinari CA). This has been a long-term issue among notable epileptologists. But, the International League Against Epilepsy (ILAE) commented that CSWS is sometimes referred to as ESES (in the Revised terminology and concepts for organization of seizures and epilepsies; Report of the ILAE Commission and classification and terminology, 2005–2009. http://www.ilae.org/Visitors/Centre/Definition_Class.cfm). Although LKS patients often present with ESES or CSWS on their EEG findings concurrent with possible cognitive abnormalities, at least some of them, their EEG abnormalities do not always reflect their auditory verbal symptoms. Hence, ESES/CSWS are electroencephalographic pattern descriptions and are not always coincidental with clinical LKS findings.

The pathophysiology underlying cognitive and behavioral disturbances in children with Landau–Kleffner syndrome or in epilepsy with continuous spike-and-waves during slow-wave sleep has been investigated (Nieuwenhuis and Nicolai 2006). There have been a few sleep studies of LKS patients. However, the recent interest in sleep studies has resulted in a discussion as to whether sleep and cognitive function disturbances, including language ability, are related (Méndez and Radtke 2001). The presence of strict abnormal patterns of sleep EEGs, as defined above, has not been examined. The records from all of the published sleep indicate that all sleep stages were present but that no specific abnormalities in sleep cycles were found. Over the long term, sequential EEGs of LKS patients showed a normalization of their EEGs (18 patients in Project B). If some abnormal findings in their EEGs persisted, at least a considerable degree of improvement in their symptomatology was evident.

Among our patients' data (Project B), about half of our LKS patients had a temporal foci abnormality and about one-third of these patients had centro-parietal to occipital foci pathology. Frontal foci pathology was determined in only one patient (Kaga et al. 2012). Bilateral or unilateral foci pathology was often recorded and occasionally these pathological foci locations moved from one electrode to another. Abnormal EEGs and clinical seizures do not always occur concurrently.

3.3 Audiometric Findings in LKS Patients

Pure-tone audiometric findings in LKS patients' are basically normal (Fig. 3.18 the left) but in the acute to subacute stages, they are sometimes normal (Fig. 3.14 left) and sometimes abnormal showing mild elevations in hearing thresholds (Figs. 3.15, 3.16 left, 3.17 upper left). Middle ear function is also normal. Nevertheless, if patients have coincident otitis media, they could be erroneously diagnosed, especially at the onset of their LKS (patient H).

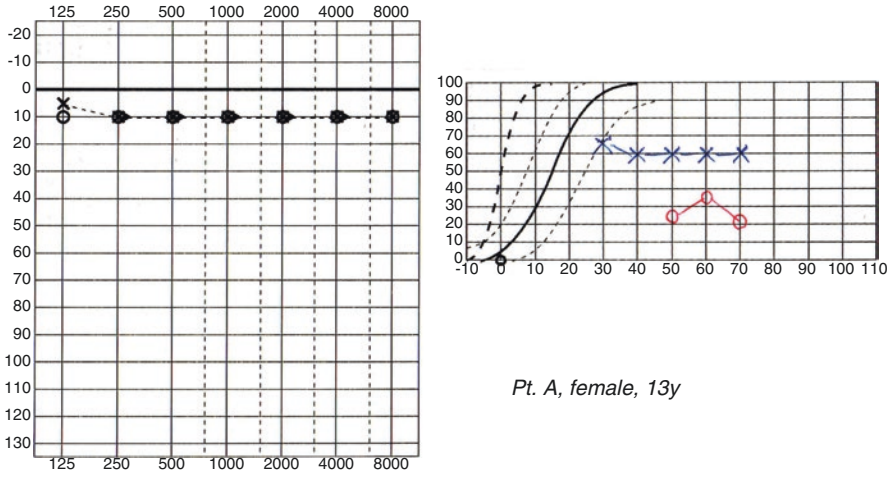
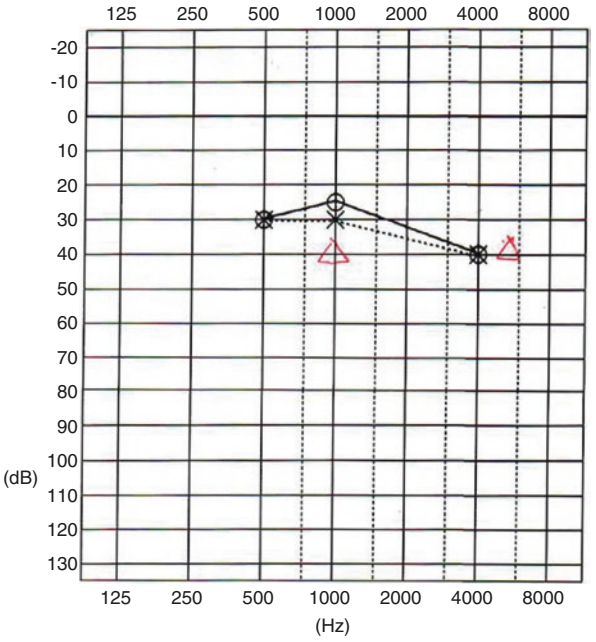


Fig. 3.14 Audiogram of patient A, 13 years old, female. Pure-tone audiometry (right ear) is normal. Word discrimination score of the left ear is depressed. In this patient left ear preponderance was apparent

Fig. 3.15 Audiogram of patient B, 4 years 8 months old, female. She responded well to environmental sounds, door bunging mother's voice, and conversation. She responded even to the whispering voice along with the ordinary level of voices. Ordinary audiometry could not be performed in her. Change of expression induced by listening to the stimuli through headphones. Circle and times symbols are for the right and left ear, respectively. Triangle is the threshold of positive response induced by warble tone induced by pediatric audiometer



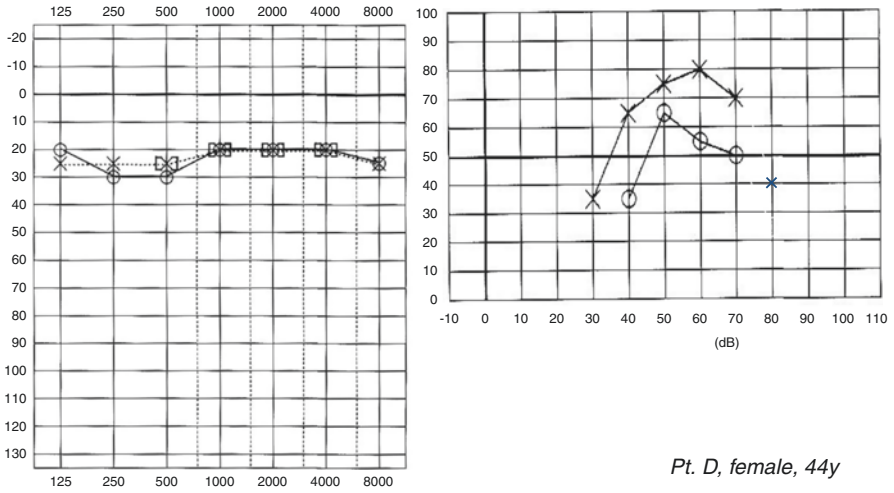


Fig. 3.16 Audiogram of patient D, 44 years old, female. Left is pure tone audiogram which shows mild elevation of the threshold (normal range). Right is the word discrimination test which shows her reduced hearing. 35% in the right and 55% in the left of discrimination at 40 dB stimuli, respectively

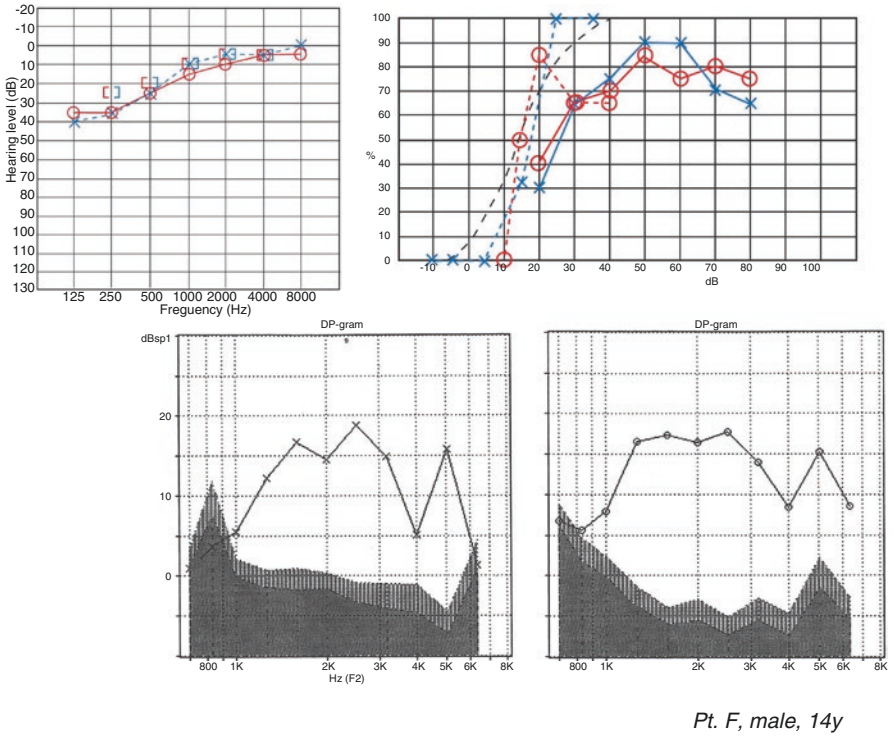
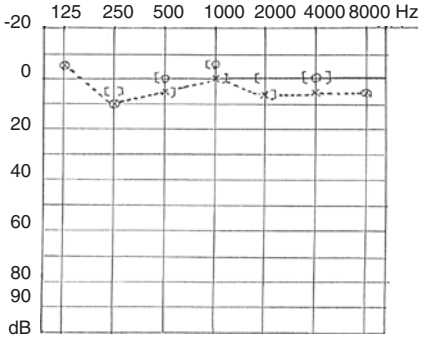


Fig. 3.17 Audiogram of patient F, 14 years old, male. Pure-tone audiogram is almost normal with a mild hearing loss in lower frequency. Word discrimination test is abnormal. Distortion product otoacoustic emission test was normal in each ear



	50dB	40dB	30dB	20dB	10dB
Right	57%	30%	57%	14%	0%
Left	71%	43%	43%	0%	0%

Pt. G, male, 7y

Fig. 3.18 Audiogram of patient G, 7 years old, male (Kaga 1991). Normal pure tone audiogram. Word discrimination is disturbed

Abnormal word-discrimination scores of LKS patients are similar to verbal auditory agnosia and this is the most important aspect of the disease. However, word-discrimination testing requires the patient' s cooperation and this is difficult to achieve during the patients' acute phase of the disease. Patient G was an exceptional case (Fig. 3.18, right). This probably underlies the historical paucity of reports in the literature regarding the qualitative and quantitative analysis of LKS patients' word-discrimination. The difficulty in patient's lives following the subacute to chronic phase is often related with the word discrimination (Figs. 3.14 right, 3.16 right, 3.17 upper right). Long-term sequela of LKS seems mainly due to the abnormal word discrimination (patient D in Sect. 6.4, Fig. 3.16). The Token test is often helpful in discerning a patient's ability to understand words, phrases, and sentences. Moreover, when LKS patients have nonverbal auditory agnosia as a complication, abnormalities in their environmental sound-discrimination test scores are often noted. These tests of verbal and environmental sound discrimination are essential in the evaluation of each patients' ability to function auditorily on a daily basis.

Sound localization was usually described as being normal in our patient survey; however, upon closer examination, a few LKS patients could not auditorily localize sound sources (patient D). Additionally, even if patients could discriminate differences in sound intensity, then they usually could not discriminate time interval differences.

3.4 Evoked Responses in LKS Patients

3.4.1 Auditory Brainstem Responses (ABR)

ABR recordings from LKS patients are usually normal (Figs. 3.19 and 3.20 upper case). An obvious caveat here is that patients who have concurrent hearing losses (conductive or sensorineural) often exhibit abnormalities in their ABR recordings. These abnormal recordings are occasionally thought to be the cause of their hearing impairment and their diagnoses can be delayed for a few months up to years.

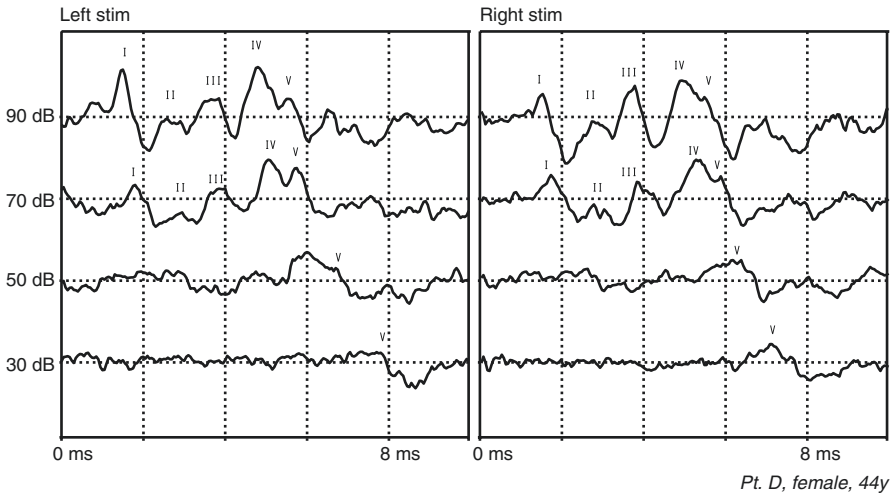


Fig. 3.19 ABR of patient D, 44 years old, female. ABR shows normal waveform, latency, and threshold in both sides of her ear

3.4.2 *Slow Vertex Responses (SVR)*

The slow vertex response (SVR), otherwise known as the long latency auditory evoked response, had been used to objectively assess hearing acuity until the recording of ABRs became available to clinicians. In the earlier literature on LKS, some patients with normal SVRs were found (Suzuki and Takeuchi 1971). Patient G showed normal SVR along with VEP (Fig. 3.20). Recent studies have often emphasized that normal ABR thresholds obviated SVR evaluation and, as such, these recordings were not often obtained.

However, one of our patients (patient A, age of 4 years old) had normal threshold ABR recordings; however, successive SVR testing was useful for her to evaluate her own discrimination of verbal 1 [a/æ] and nonverbal stimuli (tone bursts of 1 and 2 kHz) presented ad 70 dB HL at each side of the patient's ear (Kaga et al. 1999; Inagaki et al. 1996) (Fig. 3.21). These successive evaluations were highly correlated to the clinical severity in her understanding of verbal stimuli.

SVR, mismatch negativity, and P300 were induced by paired verbal and nonverbal stimuli were made from a woman's voice. Duration of the stimuli was arranged to 100 ms duration. Precise methods were already published (Kaga et al. 1982, 1994, 1999; Horimoto et al. 2002).

3.4.3 Combined Evoked Potentials (EPs) and Event-Related Responses (ERPs) in LKS Patients

Combined evoked potentials (EPs) and event-related responses (ERPs) became available to clinical medicine as a result of developments in computer technology. Because of the rarity of LKS patients, only a few clinicians have been able to record

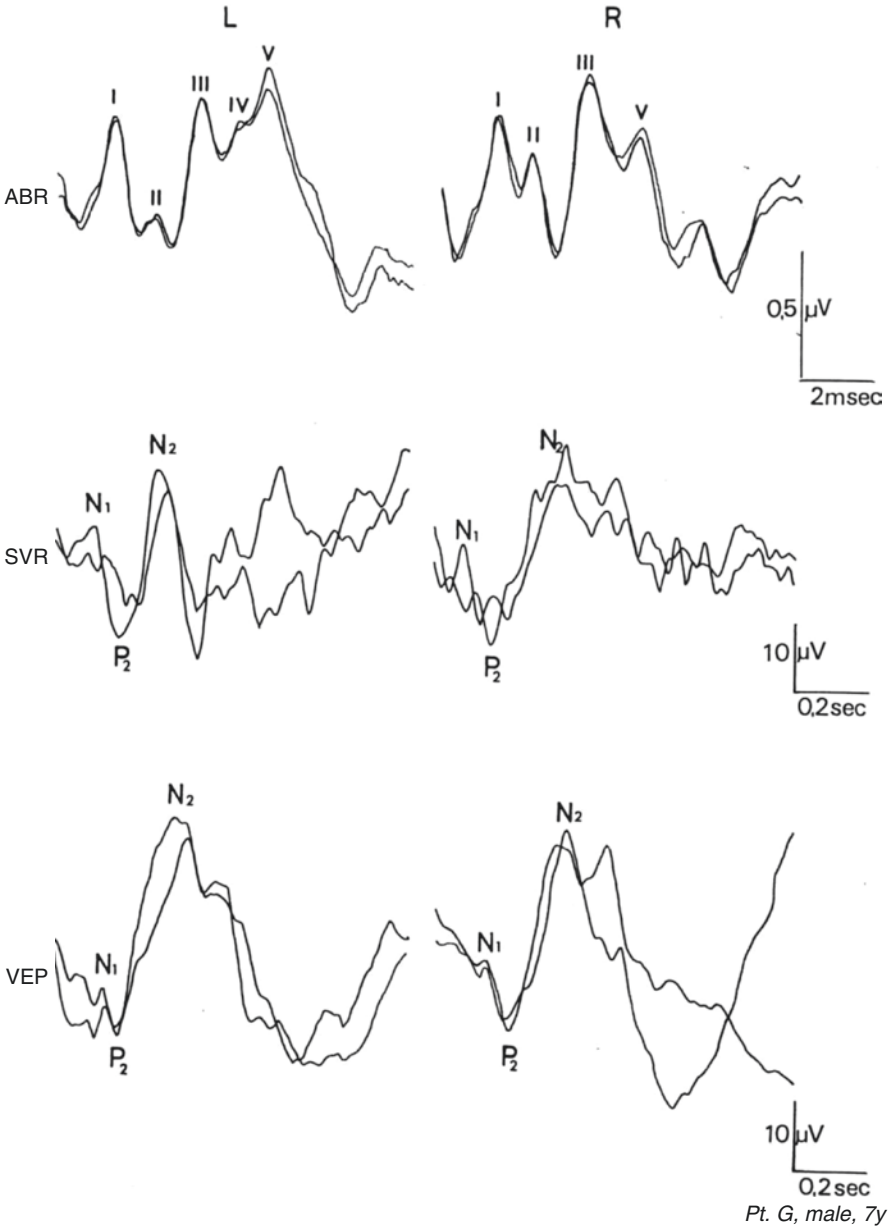


Fig. 3.20 ABR, SVR, and VEP of patient G, 7 years old, male (Kaga 1989). ABR of both sides shows normal results. Threshold was also normal. Slow vertex response was normal. However, N1 of right side was delayed. Visual evoked potential showed normal configuration with normal latencies of the waves

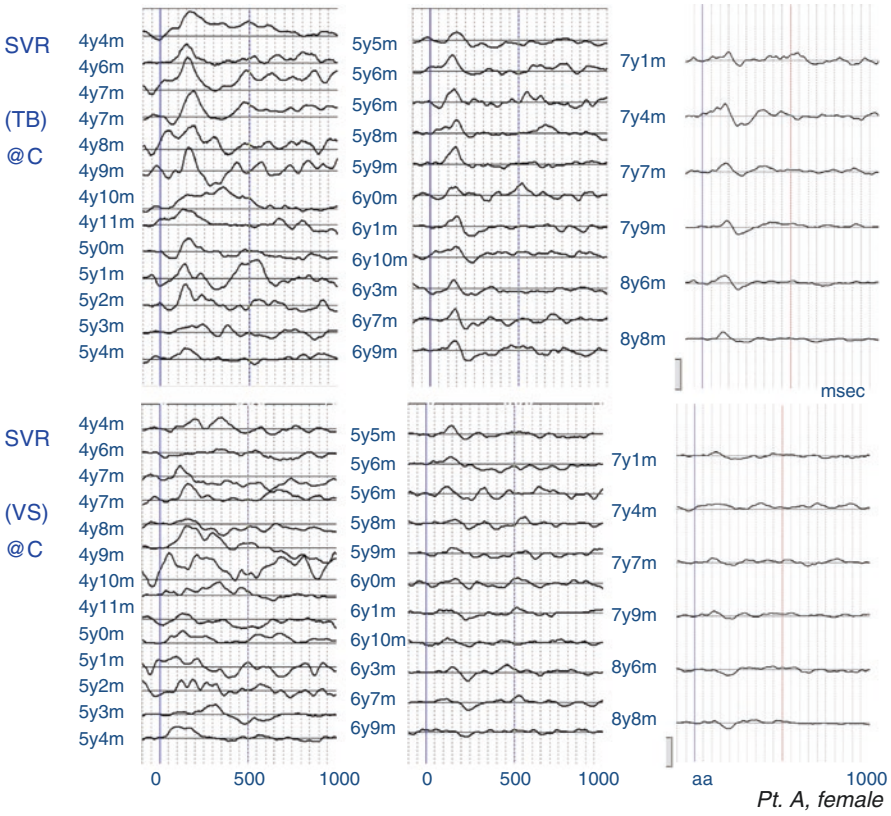


Fig. 3.21 Serial recording of SVR to non-verbal and verbal stimuli of patient A, female

and publish their EP and ERP findings of these patients to further analyze the etiology of LKS. Pyler E's team evaluated a young patient, age 2 and 1-half years, and was able to record these potentials. These recordings revealed a normal ABR configuration, normal Nas, and absent Pas in the middle latency responses of the MLRs and abnormally slow vertex responses (SVRs). On the basis of these findings, the patient was diagnosed with LKS. Plyler repeated these evaluations and he concluded that it is important to obtain the objective evaluation of ERPs, especially by audiologists, in that they were often the first specialists who were consulted regarding the deterioration of speech and language in such patients (Plyler and Harkrider 2013).

SVR, MMN, and P300 were induced by paired verbal ([a] and [æ]) and nonverbal stimuli. The precise methods were already published (Kaga et al. 1982, 1994, 1999; Horimoto et al. 2002) (Please refer also to Sect. 3.4.2).

3.5 Event-Related Potentials

3.5.1 Mismatched Negativity (MMN)

Mismatched negativity (MMN), which was discovered by Näätänen, is a negatively going potential recorded at around 200 ms following the patients' unconscious recognition of the difference between two kinds of stimuli which have subtle time gaps between their presentations. Abnormal findings in MMN latencies have been shown as evidence of a patient's inability to unconsciously discriminate between faint difference of multiple stimuli. Näätänen and his colleagues examined the MMNs of infants (Alho et al. 1990) and adults with various cognitive conditions, both normal and impaired.

Metz-Lutz and Filippini reported MMN in Rolandic epilepsy (RE) patients (16 typical and 7 atypical) (Metz-Lutz and Filippini 2006). In their article, the specific details of normal and abnormal MMN recordings were described and patients with LKS were apparently included in their study. However, the overall differences between the MMN scores of their RE (Rolandic epilepsy) patients and their LKS patients were not clearly spelled out.

Among our patients, the occurrence of abnormal MMNs increased concurrently with these patients' exacerbations of their auditory verbal symptoms. MMN (mismatched negativity) responses to aural stimuli, when presented verbally to our LKS patients, often revealed more abnormal responses than when these stimuli were presented aurally as pure tone bursts. This suggests that the discrimination of verbally perceived sounds in patients with LKS is more impaired and disturbing to them than is the perception of non-verbal sounds.

Figures are MMN of two patients with LKS (D and H) (Figs. 3.22 and 3.23). The degree of abnormality in MMNs is closely coincident with disease severity.

3.5.2 *The P300 Evoked Potential*

The P300 is an event-related potential, recorded from the scalp, and provoked by the presentation of stimuli by various modalities (auditory, visual, and somatosensory). The P300 potential was discovered and described by Sutton in 1965. He detected a large positive-going wave in the time-averaged EEG recordings of subjects which occurred around 300 milliseconds following their subjective discrimination of the difference between various parameters of two different stimuli.

In our study of the P300 responses of our LKS patients, we find that the extent of abnormalities in their P300 tracings increases concurrently with the severity of each patients' symptoms.

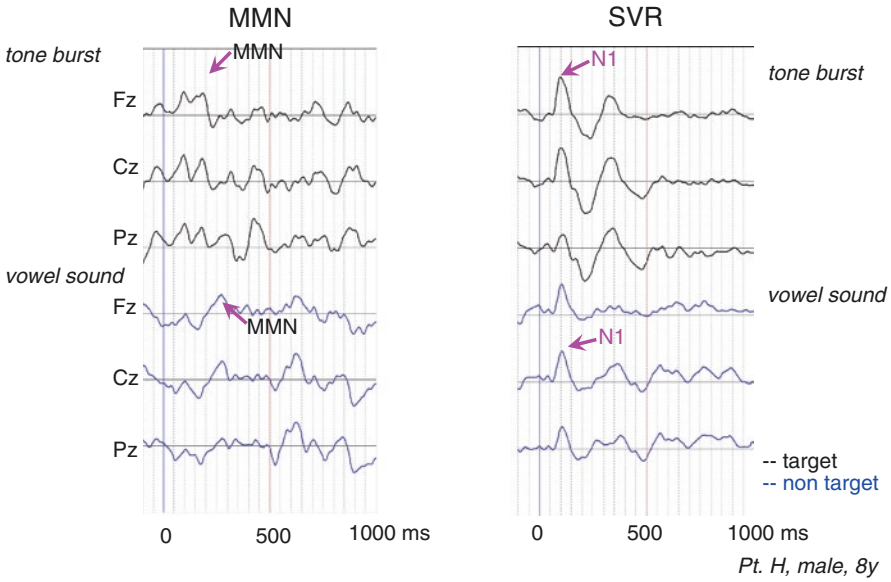


Fig. 3.22 MMN and SVR of patient H, 8 years old, male. Both N1 of SVR to TB and VS are clearly induced with a little longer latency of the latter. This is a normal response compared with the healthy subjects. MMN to TB and VS are clearly elicited with a little longer latency of the latter. Again this is a normal response confirmed by the healthy control subjects. His clinical auditory verbal symptoms were much milder than patient D

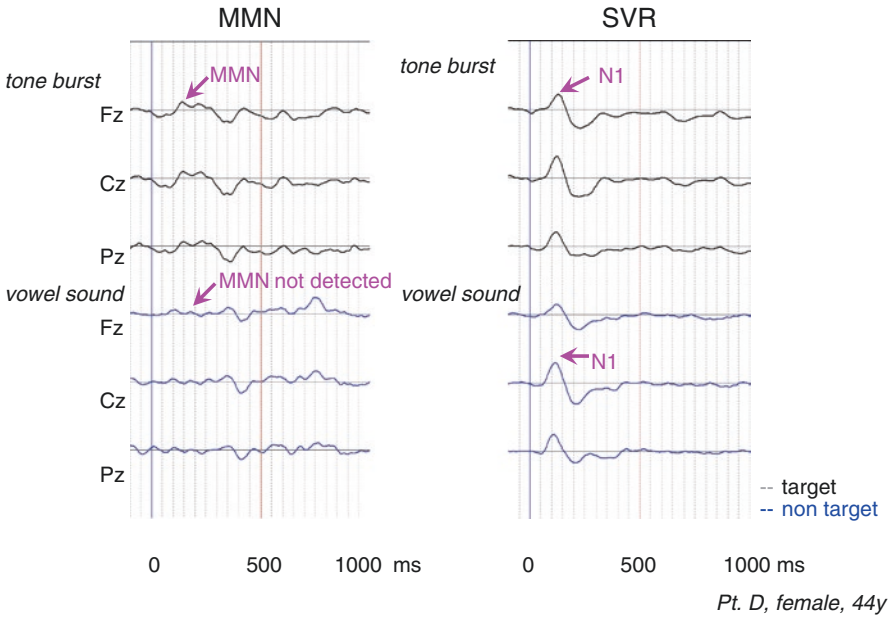


Fig. 3.23 MMN and SVR of patient D. 44 years old, female

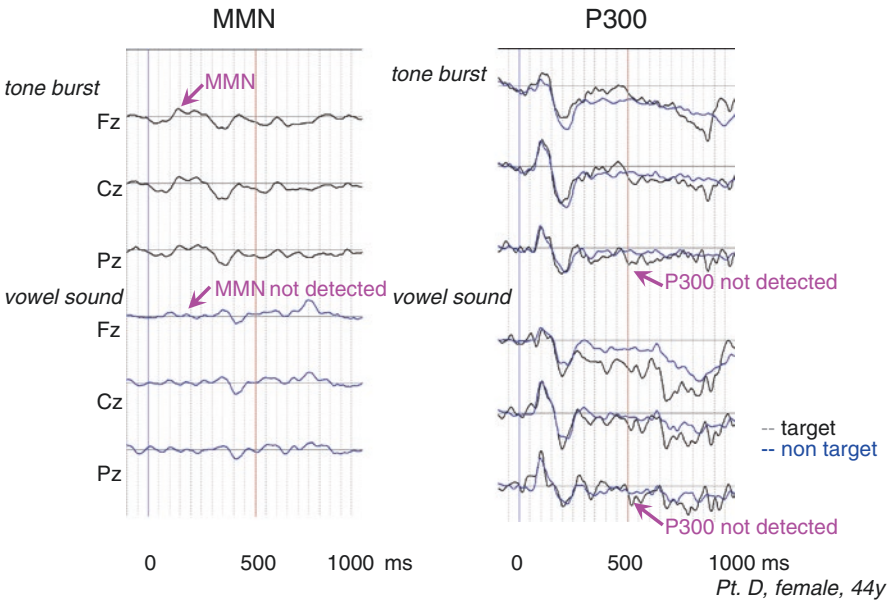


Fig. 3.24 MMN and P300 of patient D. 44 years old, female. Her P300 to TB and VS are both very shallow and ambiguous. She could not differentiate both pairs of sounds clinically

Figure 3.24 is P300 of patient D. The degree of abnormalities in P300 tracings is closely concurrent with the severity of symptoms.

3.6 Blood Exams, Urinalysis, and CSF Measures

The results of routine blood counts, blood chemistry, serum, and urinalysis are always normal in LKS patients except in patients with complicated diseases which are not related to LKS. The clinical features of LKS are often suggestive of degenerative diseases in the central nervous system and their pathogeneses have been explored for many years. Whenever new bio-analytical methods or technologies were developed and became available to clinicians these analyses, i.e., amino acids, lysosomal enzymes, and organic acids, they were utilized in the workups of LKS patients. Invariably, the results of these analyses were normal in LKS patients. Urinalysis findings were also normal. Reports in the literature from years past have indicated that cerebrospinal fluid (CSF) specimens were generally obtained from LKS patients and again, the findings were rarely abnormal. However, one report (Lou et al. 1977) of an LKS patient showed an elevation of CSF protein with accumulation in the temporal lobes as illuminated by radioisotope (RI) scans of the brain. This patient was thought to have had a possible localized encephalitis which is an entirely different pathology than LKS.

3.7 Neuroimaging Examinations

Advances in the technology of neuroimaging directly effect the clinical evaluations of LKS patients. In the past, only cranial x-rays were available to clinicians then, over the years, new technologies were developed such as: pneumoencephalography (PEG); brain echo; brain radioisotope scanning (RI); carotid angiography (CAG); computerized tomography (CT); magnetic resonance imaging (MRI); magnetic resonance angiography (MRA); functional magnetic resonance imaging (fMRI); single-photon emission computed tomography (SPECT); positron-emission tomography (PET); diffusion magnetic encephalography (MEG); and diffusion tensor infusion (DTI). Each of these technologies has become valuable in the exploration of central nervous system diseases such as LKS. Currently, some of these technologies, i.e., PEG and RI, are rarely used in research and clinical settings instead of being mostly replaced by MRIs, MRAs, fMRIs, SPECT, and PET scans.

Since computerized tomography (CAG) became available to clinicians, many LKS patients have been evaluated by this technique to visualize pathology of the middle cerebral artery and the surrounding cortical language regions such as Broca's area, Wernicke's area, and the angular gyri. Pascal-Castroviejo's group added oral nicardipine to the pharmaceutical armamentaria of conventional anticonvulsants for LKS patients. Following recovery from their disease, two of their patients showed a recanalization of obstructed vessels. The group thus inferred that the pathogenesis of LKS was focal cerebral vasculitis (Pascual-Castroviejo et al. 1992).

No follow-up studies of these or other patients have been reported. CAG has mostly been replaced by MRA and still no definite abnormalities in LKS patients have been reported.

There have been three reports of patients with LKS or LKS-like symptoms (Rapin I, Otero, Solomon). In one of these reports about the organic lesions, she detailed her findings of a patient in which she had found by CT scan a suspected small hemangioma involving the left angular gyrus with decreased blood flow to the cortical area supplied by the left middle cerebral artery. Unfortunately, she later withdrew this paper as she felt that she had over-read the scans (Rapin 1988). Another report involving an LKS patient (Otero et al. 1989) offered a diagnosis of cysticercosis, again near or around the angular gyrus. In 1993, Solomon et al. contributed their findings to the literature of an LKS patient in whom they found a cystic astrocytoma involving the hippocampus. On their reported reading of a CT scan of this patient, these clinicians observed a large arachnoid cyst involving the anterior half of the left temporal lobe. Solomon et al. postulated that this was an incidental finding and that it was not a causative pathophysiology underlying LKS. It is unlikely that the pathophysiologies of the two above reported cases are indicative of the true etiology of LKS. With the exception of two reports in the literature, there have been no reports of LKS patients which outline definite and or localized structural abnormalities. One of our patients with LKS had, incidentally, a large arachnoid cyst on the tip of his left temporal lobe (Fig. 3.25). We elected to not surgically remove this cyst but, nevertheless, the patient completely recovered from

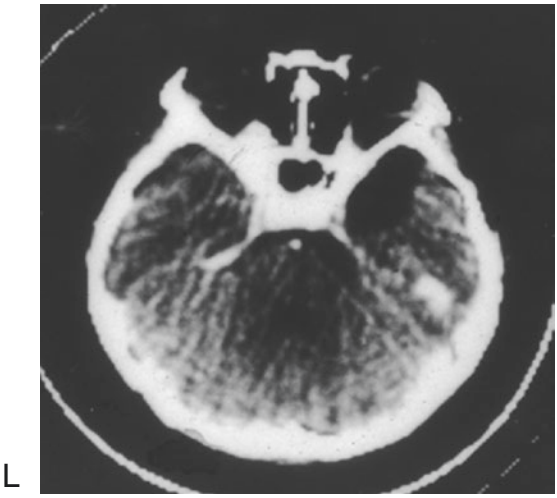


Fig. 3.25 CT scan of patient E. The quality of imaging was extremely low because it was the CT scan of pioneering age along with his body motion. However, arachnoid cyst in the right temporal tip is definitely present

his typical LKS within a few years of its onset and he is now a successful businessman.

Sieratzki et al. described their functional MRI findings in a patient with LKS (Sieratzki et al. 2001). They found extensive bilateral (R>L) auditory cortical activation when the patient listened to the speech. This cortical activation did not appear when the patient listened to music nor did this activation appear when the patient was involved in silent lip-reading. When the patient was observing and interpreting British sign language, of which he was very adept at, fMRI revealed activation over various temporo-parieto-occipital association areas of the cortex. These findings indicated that for each different type of stimulus input (auditory visual, i.e., music, live speech, or lip-reading), a corresponding unique area of cortical activation can be defined.

3.7.1 SPECT and PET Scan

In 1993, Mouridsen et al. presented their case of a 5-year old patient with LKS and who showed decreased 99mTc-hexamethylpropyleneamineoxime (^{99m}TcHMPAO) activity in her left middle frontal gyrus and right mesiotemporal/hippocampal areas. This patient's EEG changes were also localized over these same areas.

Harbord et al. (1999) evaluated 5 patients with LKS, between the ages of 2 and 5, with ^{99m}TcHMPAO-SPECT. Two of their patients exhibited reduced activity within their temporal lobes: one on the left side and the other on the right. Of the remaining three patients, hyper-intense focal activity was found, in the ictal phase, over and within the left posterior temporal area of their cortices, i.e., over Wernicke's area.

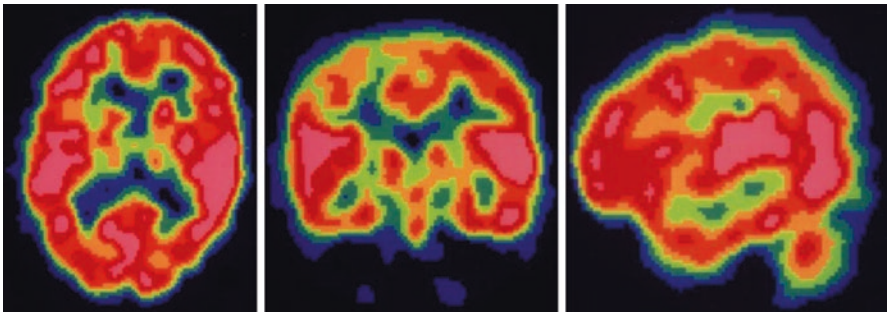
There have been a few published reports presenting the findings of PET scans of LKS patients. In general, the PET scan is utilized to visualize epileptogenic areas of cortical regions (Hammers et al. 2001; Muzik et al. 2000).

Shiraishi et al. (2007) analyzed ^{18}F-fluolo-D-glucose (FDG), ^{11}C-Flumazenil (FMZ)-PET, ^{99m}TcHMPAO-SPECT, and magnetoencephalography (MEG) findings in an 8-year-old female patient with LKS both before and after medication had effectively controlled her disease. They found that abnormalities involving the tip of the left temporal lobe play an important role in the pathogenesis of LKS. They based their conclusion on their findings after presenting stimuli to their patients via various modalities, i.e., music, live speech, or lip-reading.

An EEG taken during sleep at an earlier disease stage of Shiraishi's patient demonstrated continuous diffuse spike and wave complexes predominantly over the left centro-temporal region. SPECT data showed hypoperfusion within and over the whole left frontal lobe and over the left occipital lobe. In a follow-up SPECT study of this patient, the hypoperfusion was generally diminished, especially within the left temporal lobe. Decreased glucose metabolism was noted, by ^{18}F-FDG-PET, in the bilateral medial and superior regions of the left temporal lobes. A subsequent PET scan follow-up at 9 months indicated that this decreased glucose metabolism was mostly ameliorated. However, the other noted effected cortical areas remained unchanged. ^{11}C-FMZ PET scans suggest that the loci of pathophysiology in LKS patients lie within the tip of the left temporal lobe.

The commonality of the effected cortical regions reported in these PET scan studies of LKS patients, which similarly localized reduced activity, implies that at least some part of the temporal lobe, especially the perisylvian area, is involved in the pathophysiology of patients with LKS. However, it is not entirely clear that these findings explain the cause nor the clinical findings of LKS.

One of our LKS patients underwent SPECT evaluations and presented abnormal findings (Fig. 3.26).



Pt. A, female, 14y

Fig. 3.26 SPECT scan of patient A at her acute stage of the disease (with ^{99m}Tc-ECD). Decreased blood flow in bilateral temporal lobes, left lateral and medial frontal lobe, and left thalamus was reported. Average blood flow of the brain was also decreased

3.8 Magnetoenechalography (MEG)

Paetau et al. in 1991 published their MEG findings of a patient with LKS. They recorded spikes which originated from around the left auditory cortex. Evoked responses (ABRs) were suppressed during right ear stimulation but recovered when the patient's spikes ultimately disappeared over time. These authors reasoned that unilateral discharges at or near the auditory cortex disrupted auditory discrimination in the effected hemisphere and led to the suppression of auditory information from the opposite hemisphere. They also postulated that the symptoms of LKS, epileptic discharges, and auditory agnosia could be explained on the basis of their findings.

Paetau et al. (1999) published a subsequent paper outlining their EEG and MEG findings in four patients with LKS. They found that in all of these patients their abnormal epileptic activity began within the intrasylvian cortex. One of these patients had additional epileptic activity which spread over the contralateral sylvian cortex. Secondary spikes were sourced to the ipsilateral perisylvian, temporo-occipital, and parieto-occipital areas. In two of their patients, epileptic activity began from a single intrasylvian generator. Their remaining patients all had independent left and right hemisphere epileptic activity or focal spikes (Paetau et al. 1999).

A decade later, Paetau in 2009 published MEG findings in 28 patients, ages between 3.5 and 12.0 years, with LKS. More than 80% of them showed bilateral epileptic discharges which were generated in the perisylvian cortex. This cortical area is involved in auditory and language functions. The remaining 20% of these children had a unilateral perisylvian epileptic generator which triggered a secondary bilateral synchronicity of their spikes. Paetau mentioned that this 20% patient cohort might possibly benefit from multiple subpial (below the pia matter) ablations of the perisylvian epileptic generator area. Paetau stressed the importance of the use of MEG in the clinical evaluation of LKS patients.

Sobel et al. in 2000 employed MEG analyses in their study of 19 patients, aged 4–14 years, who were suspected of having LKS, and disclosed the results (Sobel et al. 2000). A seventy-four channel system was used in their study. Thirteen of these 19 patients (68.4%) produced perisylvian spikes. In 10 of these 19 patients, bilateral spikes were produced and 3 had unilateral spikes. Of the remaining six patients, four produced non-sylvian spikes and in two of them no spikes were noted.

In an analysis of the data from the above-cited studies, three patients were found with unilateral spikes and they were then divided into two groups: one patient with spikes on the left side and two patients with spikes on the right side. However, one of those patients with right side spikes was suspected to not have had LKS. Four other patients found in this data analysis produced non-sylvian spikes: one with bilateral middle-frontal gyrus spikes, one with left central and parietal spikes, one patient, whose diagnosis of LKS was doubtful, produced right parieto-occipital spikes, and one patient, whose symptoms did not clearly differentiate LKS from autism, produced left middle-frontal gyrus spikes. Two patients in this overall data analysis did not display spikes: one patient was not able to be tested because of a lack of cooperation, the other had a questionable diagnosis of LKS. Thus, Sobel

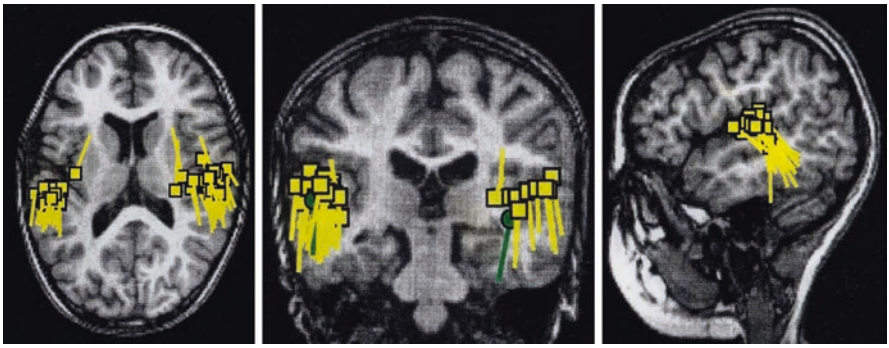


Fig. 3.27 MEG of patient A at her acute stage of the disease. Dipole was found in bilateral temporal lobes

et al. appeared to implicate perisylvian spikes or left-sided spikes as diagnostic of LKS.

Although these studies pointed out that the frequency of sylvian spikes was rather high, the recording of these spikes did not seem to be an inevitable sign in the diagnosis of LKS in that our MEG examinations of three patients with LKS showed different spike activity.

Some of our patients who underwent MEG examinations gave abnormal results. Figure 3.27 is a MEG result of patient A in her relatively acute stage of her disease.

Overall, this data analysis seemed to indicate that abnormal findings might be related to and vary with the disease stage. It should be noted that MEG evaluation is not routinely available in the ordinary clinical situation.

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Chapter 4
Etiology and Genetics

4.1 Morphological Approach

4.1.1 Gross Anatomical Approach

In most reported LKS patients, CT and MRI scans showed no intracranial lesions which might cause their auditory language symptoms. Gross anatomical lesions have been basically ruled out as the etiology of Landau–Kleffner syndrome. Nevertheless, historically arachnoid cysts (De Volder et al. 1994), astrocytomas (Solomon et al. 1993), and cysticercosis of the brain (Otero et al. 1989) have been implicated in the pathogenesis of LKS.

De Volder et al. in 1994 performed a cyst-peritoneal shunt on a 10-year-old boy 5 years after the onset of his symptoms because his residual symptoms had not been relieved by anticonvulsants nor by various speech therapy techniques. Although his CT and MRI scans did not reveal any mass effects due to his cyst, glucose enhancement during his PET scan indicated increased epileptic activity especially over the inferior frontal gyrus and the perisylvian areas. Eight months postoperatively this patient's language function was evaluated and his improvement was remarkable. This excellent outcome could have resulted from a successful surgical intervention but his improvement due to the natural course of his disease could not be definitely ascertained.

Undeniably, there exists the possibility that space-occupying lesions and symptoms such as found in LKS patients happened together and improvement of symptoms was just a natural course of their disease.

The relationships between these LKS patients with any of the above-mentioned anatomical lesions seem plausible and these patients should be monitored and described in the literature to advance future research. However, morphological abnormalities, per se, as reported over the last half century have been unsuccessful in delineating the actual pathogenesis of LKS.

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Of course, if functionally responsible lesions are concurrent with organic lesions and they both have the same recorded electrical effects, then the loci of LKS pathophysiology could arise from anatomical alterations such as from space-occupying lesions.

4.1.2 Microscopic Approach

Many clinicians have, over the years, tried to delineate the etiology of LKS. Brain biopsies (McKinney and McGreal 1974; Lou et al. 1977) and other surgical specimens obtained (Cole et al. 1988) have shown non-specific microscopic changes and did not point to the presence of definitive anatomical abnormalities in this disease.

Lou et al. in 1977 found inflammatory cell infiltrations in the temporal lobe from a brain biopsy in one of their four patients who had aphasia and epilepsy. They speculated as to the presence of an inflammatory process in LKS; however, this has not been subsequently confirmed to be the case. Cole et al. in 1988 published a report of two surgically treated LKS patients who had no pathological changes despite their careful microscopic analysis. Hence, the only remaining possibility, at present, seems to be that a functional abnormality is responsible for the symptoms of LKS.

In some medical facilities, the resection of various neuronal connections has been attempted in LKS patients (Morrell et al. 1995) but no unique pathological abnormalities, such as an inflammatory process, have been detected. Thus, Lou's patient described above was a very exceptional case which was not a "typical" LKS patient. LKS is not a fatal disease and thus, surgically obtained cortical specimens have been studied from these living patients but no postmortem microscopic studies of brain pathology in LKS patients have been published in the literature.

4.2 Present Status in Delineating the Etiology of LKS

Presently, the etiology of LKS has yet to be determined. Morphological cerebral abnormalities have essentially been ruled out. Functional abnormalities are emerging more and more lately as the possible etiological basis of LKS. Thus, most clinicians today attempt to find a relationship between LKS and epileptic disorders, especially those arising from temporal lobe dysfunctions. A part of MEG studies showed localization of spike foci such as left temporal dominancy (Shiraishi et al. 2007) and deep sylvian sulcus (Sobel et al. 2000). The pharmacological effectiveness of steroids and immunoglobulin therapy in improving the language function of LKS patients has prompted investigations of a potential immunological factor indirectly involved in the etiology of LKS. However, when one considers the rarity of familial cases, it is quite unlikely that LKS is not a genetically heritable disease.

Lately, the trend to explore gene mutations in LKS has slowed down a bit but it still continues to go on.

4.2.1 LKS and Autism Spectrum Disorder (ASD)

There are children who have lost their ability to develop speech and this has led to regression in their overall development. This apparent similarity between LKS and some ASD patients has drawn the attention of clinicians to further elucidate this relationship. In fact, some LKS patients demonstrate very similar behaviors to those of autistic patients. Recent emphasis has been directed toward autistic regression. In the International Classification of Diseases, tenth version (ICD-10), the F8 code describes disorders of psychological development and includes the F84 code of pervasive developmental disorders. The F84.3 code describes other childhood disintegrative disorder. The Diagnostic and Statistical Manual of Psychiatric Disease, version IV (DSM-IV) also includes this pathological state of childhood disintegrative disorder. In the past, this categorization was referred to as "Heller's dementia" or infantile dementia.

Rapin (1965) reviewed the literature and she concluded that Heller's dementia is not a single disease entity but instead a disease having multiple etiologies.

4.2.1.1 Autistic Regression and Language Regression

Autistic regression was first described by Eisenberg L and Kanner L in 1956. Initially, this was thought to have a rare occurrence but gradually it became recognized as a fairly common disorder. Regression in both language and behavior in patients with autism (seen at ages between 18 and 36 months) has been reported to occur in 22.4% of such patients by Wakabayashi (Wakabayashi 1974) and occurring at least a third of autistic toddlers regress in language, sociability, play and often cognition by Rapin (Rapin 1995). Regression of autism was thought to be related to Heller's disease by Chmiel (Chmiel and Mattson 1975) and he later named this autistic regression as "disintegrative disorder of childhood" (DDC). DDC is described as a severe loss of social and language skills in children aged 2–4 years. DDC is included in both the DSM-IIIR and DSM-IVTR under the rubric of pervasive developmental disorders. In DSM-5, DDC is placed in the category of autism spectrum disorders. Stefanatos, in 2002, suggested that there is considerable similarity between the symptoms of autism spectrum disorder and those of LKS. Kurita, in 1985, 1992, and 2005, has, over the years, explored this loss of speech concurrent with behavioral regression in patients with autistic disorders. This clinical similarity of the symptoms of the deterioration of language in LKS resulted in it being thought of as an autistic disorder. The ICD-10 assigned LKS with the code G40.8 (Specific developmental disorders of speech and language) and the ICD ruled out acquired

aphasia from a known etiology including childhood autism (F8.0, F84.19 and other integrative disorders (84.3)).

LKS and autistic disorder are categorized as different diseases. However, the syndromes of both are associated with the symptoms of epilepsy. Deonna in 2009 explored this relationship between autism and LKS from the point of epilepsy and epileptic electroencephalographic abnormalities.

In conclusion, no clear cause and effect relationship between LKS and autism has been established. However, some LKS patients do show autistic tendencies at least when they are having severe communication disorders. One of my patients displayed typical autistic symptoms after he had acquired LKS and displayed behavioral changes as a sequel of his LKS. His preclinical symptoms were not fully documented but, according to the DSM-IVTR description, his autistic symptoms were not present during his early childhood and only appeared after he developed LKS. The case report of this patient is presented in the case report section (Patient F). He was precisely evaluated by PARS (the Pervasive Developmental Disorders Autism Society Japan Rating Scale). This questionnaire is designed such that the caregiver can catalog the presence of their children's past and present symptoms which suggest autism. The questionnaire was assembled by a special team of Japanese professionals in the field of autism and it was published by the Japan Autism Society.

4.3 Current Genetic Research

The recent development of molecular biology has inspired a lot of competition in the localization of genes and in their expressions in all areas of medicine. The field of epileptology seems to be no exception. Roll et al in 2006 identified the gene *SRPX2* (*Sushi Repeat Containing Protein, X-Linked 2*) which is the gene that induces Rolandic seizures and is related to speech and cognitive impairment. In addition, they found that the *SRPX2* gene and the *ELP4* gene (elongated acetyltransferase complex, subunit 4) were both associated with childhood epilepsies in terms of cell motility¸ migration, and adhesion to their molecular bases.

Rudolf et al. also described the genetic features common to both LKS and CSWS in terms of language and cognitive deficits (Rudolf et al. 2009). In their article, they indicated that although benign childhood epilepsy with centro-temporal spikes (BCECTS) or benign Rolandic epilepsy had been classified as different disease entities from those of LKS and CSWS, they included their four patients as a single continuous spectrum of disorders.

Electroencephalographic studies have shown that some LKS patients have focal epilepsy, epileptic encephalopathy with ESES or CSWS during LKS. These patients show centro-parietal spikes in their EEG findings. Some researchers in molecular biology have, thus, focused on idiopathic focal epilepsy which shows Rolandic spikes but then *GRIN2A* gene was discovered (Lemke et al. 2013). *GRIN2A* is a

gene which codes for the protein GluN2A which is an α subunit of N-methyl-D-aspartate (NMDA) glutamate receptor. Lemke et al. discovered new mutations in the *GRIN2A* gene in two independent cohorts (27/359). Among their patients with a more severe type of CSWS (continuous spike waves in slow sleep), 17.6% of them had a higher incidence of mutation of the *GRIN2A* gene than in those patients with a mild type of CSWS (BECTS, 4.9%). Exon-disrupting microdeletion was found in 3 of these 286 patients (1.0%). On this basis, the authors concluded that mutation of the gene encoding the NMDA receptor, NR2A subunit, was a genetic risk factor for idiopathic focal epilepsy. This research was revealing to but not intended for the study of LKS itself.

Turner et al., in 2015, reported that 20% of their patients with epilepsy-aphasia spectrum (EAS) revealed *GRIN2A* gene mutations and those patients with these mutations showed obvious speech and language symptoms. The authors proposed that this finding might assist in the diagnosis of LKS. In addition, and regarding EAS, they found copy number variation (CNV) in molecules related to this RNA binding and to cell adhesion. At this point in time, the *GRIN2A* gene is considered to be the gene involved in language disorders and epilepsy. However, the *GRIN2A* gene is not the only responsible one to induce LKS and typical LKS patients without abnormalities of their *GRIN2A* gene have been found. Of course, not all of the patients with an abnormality of their *GRIN2A* gene have LKS. Genetic evaluations of patients with defined LKS have only just begun.

Among our patients, the most typical patient of LKS with long-term follow-up (Patient D) was examined by molecular biology techniques. No abnormalities were observed in *GRIN2A*, *ELP4* nor in other possible epilepsy/language-related genes. (These genetic findings were determined by courtesy of Dr. Mitsuhiro Kato (Syowa University) and Dr. Naomichi Matsumoto (Yokohama City University.))

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Chapter 5
Treatment and Long-Term Prognosis

5.1 Epilepsy

Anticonvulsants are administered relative to the seizure types. In LKS, focal seizures have been reported to be common but any type of seizure can occur. Thus, the targets of these anticonvulsant medications have often been focal epilepsy and occasionally primary or secondary generalized epilepsy.

Conventional anticonvulsants to relieve LKS patients' seizures usually work well when these drugs are administered specifically for each seizure type and almost all of such patients become seizure-free prior to reaching late adolescence. On the other hand, patients who did not respond to anticonvulsant medication have often been less described in the literature (Park 2003; Lagae et al. 1998; Morrell et al. 1995).

Gascon noted that some of his patients showed improvements in their EEGs following diazepam infusions (Gascon et al. 1973). Subsequent to his finding, a number of studies have reported this diazepam-related EEG improvement in some of their patients (Tsuru et al. 2000; Mikati and Shamseddine 2005; Devinsky et al. 2014). Thus, some clinicians have administered oral diazepam or clonazepam to alleviate their patients' seizures. However, oral benzodiazepines were not found to be as effective as intravenous infusions. The effectiveness of ameliorating auditory verbal symptoms is exceptional relative to steroid therapy.

Historically, the use of anticonvulsants has changed considerably due to the introduction of newly developed medications. Before the 1960s, the variety of available anticonvulsants for generalized/focal seizures was limited to phenobarbital (PB) and phenytoin (PHT). And trimethadione was the only drug for petit mal epileptic seizures. Then the anticonvulsants ethosuccimid (ESM), acetazolamide (AZA), sulthiam, zonithamide (ZSM), the benzodiazepines (diazepam (DZP), clonazepam (CZP), nitrazepam (NZP)), midazolam and clobazam, valproate (VPA), and

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carbamazepine (CBZ) were developed and have often been used for the treatment of various generalized and focal epilepsies keyed to the patient's seizure type.

Recently, gabapentine (GAB), topipramate (TPM), lamotrigine (LTG), levetiracetam (LEV), peranpanel (PER), and lacosamide (LCM) were introduced and have been used rather commonly as the second or even the first choice of anticonvulsant therapy in controlling epileptic seizures. The times of the introduction of these drugs differ within different countries. In Japan, official permission for the clinical use of these new drugs was somewhat delayed but has recently improved. As such, the use of these new anticonvulsants corresponds to the new examination techniques already mentioned in Sect. 3.6 (blood exams, urinalysis, and CSF measures).

It has been shown that patients with temporal lobe epilepsy display memory and/or language dysfunctions (Mayeux et al. 1980). In the past, such patients had been mainly treated with PHT, primidone (PMD), and carbamazepine (CZP). Recently, the first choices of anticonvulsant medication are levetiracetam (LEV) or lamotrigine (LTG) and they have both been shown to be effective.

In the treatment of auditory verbal symptoms, anticonvulsants are usually not effective. However, steroid therapy, especially pulse therapy of methylprednisolone at an early stage of LKS, is often effective. Thus, steroid pulse treatment has become the first treatment choice during the acute phase of LKS. The typical regimen is to administer 20 mg/kg methylprednisolone via an intravenous infusion for 3 days within 1 week and to repeat this cycle three times (Kamimura et al. 2004). This treatment technique is referred to as pulse therapy. Bast et al., in 2014, reported that the positive response rate of steroid pulse therapy was found in 11 out of his 15 patients (73%) who had continuous spike-waves in slow sleep (CSWS) or the Landau–Kleffner syndrome. Usually, following pulse therapy, oral steroids are prescribed for days, weeks, or even months dependent upon each patients' clinical status and based on the clinicians' insight and experience. Some clinicians opt for the use of ACTH (adrenocorticotropic hormone) rather than administering steroids.

Figure 5.1 shows the marked improvement of EEG after three rounds of 3 days successive intravenous treatment of methyl-prednisolone in patient A. However, her auditory verbal symptoms did not improve by this treatment. This phenomenon often occurs in this treatment for patients with LKS (Fig. 5.1).

Table 5.1 of our Project B study illustrates the variety of clinicians' choices in the use of antiepileptic medications.

5.2 Surgical Interventions in the Treatment of LKS

In 1995, Morrell et al. reported their findings regarding their results following multiple subpial intracortical transections (MSTs) as a treatment for removing cerebral epileptic foci. Their procedure involved ablation of the transverse fibers while sparing the vertical pathways in the cortex. Following the evaluation of 54 LKS patients in their clinic, they used the MST technique to evaluate 14 of their LKS patients and

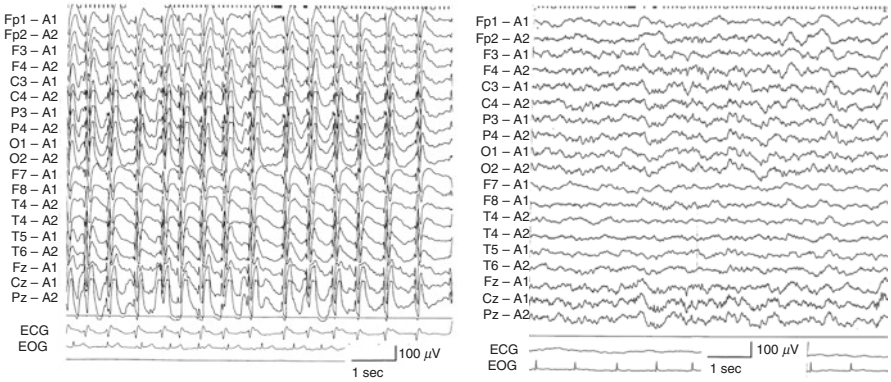

Fig. 5.1 Before (left) and after (right) treatment of methylprednisolone pulse therapy. Both asleep record in patient A. Maximum spike-wave index was less than 85% in all her disease stages. After treatment, her EEG was remarkably improved

Table 5.1 Antiepileptic medication status of LKS patients (Project B)

	Male	Female	Total
Anticonvulsants			
Carbamazepine	11	7	18
Valproate	20	10	30
Phenobarbital	3	0	3
Diphenylhydantoin	4	2	6
Zonisamide	4	3	7
Diazepam	7	2	9
Clonazepam	8	5	13
Acetazolamide	1	5	6
Phenytoin	0	1	1
Nitrazepam	1	0	1
Ethosuximide	3	5	8
Topiramate	2	5	7
Lamotrigine	1	1	2
Gabapentin	1	4	5
Immunoglobulin	1	0	1
Clorazepate	1	4	5
Steroid therapy	10	7	17
Oral	8	1	9
Pulse therapy	10	3	13
Others	2	0	2
Steroid type			
Prednisone	4	1	5
Methylprednisolone	5	1	6
ACTH therapy	5	5	10

followed them up over 13–78 months post surgery. Seven of these 14 surgically intervened patients regained normal speech and had no seizures. Five of their patients had improvement in their speech, again with no subsequent seizures and three patients showed no change in either speech or seizure activity. Subsequently, Grote et al., in 1999, published their findings of MST in 14 young patients with LKS. Grote and his coauthors were Morrell's colleagues and Grote's 14 young patients were included in the above Morrell's 10 patients. The language ability of all of these patients was evaluated by two standardized tests: the revised Peabody Picture vocabulary test (PPVT-R) and the revised expressive one-word picture vocabulary test (EOWPVT-R). Results from the PPVT-R test were obtained from 13 of these young patients: 7 patients showed good language ability, 5 gave unstable results, and 1 patient showed a decline in language ability. The revised one-word picture vocabulary test (the EOWPVT-R) was administered to 14 of these patients, of which 8 showed a slight improvement in language ability, 5 were unchanged in this regard, and 1 patient's language ability worsened. Eight among these 14 children ultimately received special support at school. A significant improvement in either of these test scores was noted in "only" four of these children. On the basis of those two reports, MST (ablative surgery) seems to impede the propagation of epileptic seizures loci onto the broad cortical language areas and thus, MST has a certain advantageous effect in terms of the long-term course of this disease.

A young girl, 4 years old, who underwent a right temporo-parietal resection was described by Fine et al. in 2014. Based on their method of superimposing their findings of SPECT and MRI, they found no focal epileptic loci and she became symptom-free.

Cross et al. in 2009 described their surgical invention on ten LKS patients at the Great Ormond Street Hospital in London, England for Children. They reported that ten of these children who had undergone MST, seven of them improved in their language ability but they never recovered to normality. The authors concluded that collaborative studies of the multiple loci of LKS are indispensable to finally delineate the etiology of LKS.

Because our patients visited our clinic at a relatively long time ago, none of our patients underwent surgery for their treatment of LKS.

In times past, the etiology of LKS was thought to be due to a functional ablation of the auditory and language cortices by epileptic seizures (Landau and Kleffner 1957). If it was correct, then the MST surgical ablation procedure should be an effective treatment methodology for LKS patients.

5.3 Speech and Language Training

LKS is a combination of a neuropsychological disorder, the symptoms of which are auditory verbal disorders, and apparent or subclinical epileptic seizures. Thus, treatment protocols should be directed toward both aspects of this disorder. Treatment protocols applied to epileptic disorders were described in the previous section.

Auditory verbal abnormalities cause speech difficulties at any age but especially in school-aged children during the acute stage of their disease. The acute symptoms of LKS are often mistaken for either hearing impairment or for a psychological disorder. Thus, caregivers of such children often initially send them to an ENT physician only to be told that their hearing is normal. Even more often than this, these children may end up being cared for by a psychologist as opposed to a pediatrician.

We at first strongly recommend that LKS patients should initially be supported to consult a pediatrician or a child neurologist and to further seek intervention by a speech pathologist and from their school teachers soon after their acute symptoms are controlled, though many patients perfectly recover without sequelae in auditory verbal symptoms. The importance of this is to improve communication and comprehension between these patients and their parents and other people around them, their families, friends, and anyone involved with their care. It is also essential to determine each patients' tentative therapy goals and their emotional state. In terms of lifelong objectives, it is especially important that these young children obtain and cultivate their vocabulary. Sign language is often useful in communicating with LKS patients and it does not interfere with their reacquiring oral language as is often the case in children with profound congenital sensorineural deafness. Thus, as Deonna et al. in 2009 have previously emphasized in Epilepsia, early training in sign language for LKS patients is commonly very helpful.

Auditory verbal symptoms in LKS patients sometimes persist into adulthood unaccompanied by intellectual deterioration. Hence, speech pathologists and teachers should maintain long-term relationships with their LKS patients to not only provide education and training but also provide continuing emotional support and to motivate them to learn and to live active lives. At the earliest stage of LKS, it appears to be difficult to begin any training due to the unstable disease condition. However, once this unstable condition resolves caregivers should immediately begin to search for ways to communicate with their patients. Communicating visually often produces a good outcome but any methodology is worth exploring.

School-age children with LKS often need special education particularly if auditory verbal symptoms are on-going. When the vocabulary of these children is severely impaired, special schools or classes for the intellectually impaired are essential. In Japan, each city's Board of Education decides which school or class each LKS child will attend, this after discussions with their guardians. Schools or classes for the hearing impaired are basically for children who have significant sensorineural hearing losses and not for central hearing impairments as found in LKS children. Thus, to maintain and improve speech, an appropriate choice of schools would be one that has a class for the hearing impaired. Teachers at such schools are uniquely specialized in working with children who have peripheral hearing losses and, in most cases, are unaccustomed in working with children with central hearing losses.

Regarding schools or classes for the intellectually impaired, teachers should realize that children with LKS are not intellectually retarded but may seem to be so because of their difficulty in comprehending and acquiring new vocabulary.

The use of visual training (sign language) in education is frequently found to be effective when working with both auditorily and intellectually impaired children. Careful observation of these children, such as detection of subtle signs of residual auditory capacity, is necessary and caregivers should encourage these children to use oral language. As improvement progresses, these children should be gradually introduced to auditory/verbal training at their school and in their daily lives. In some cases, changing a child's educational setting from intellectually impaired to hearing impaired or even to mainstreaming may be a better option. If a child makes a school change he/she may often need to be shielded from harassment by their classmates.

More than half of LKS children completely recover. The remainder maintain at least some degree of residual symptoms over the long term and some have severe sequelae. Thus, teachers and parents of these children should be repeatably interviewed as the decision to transfer a child to a mainstream setting or to remain in a school for the hearing impaired or the intellectually impaired should be based on the current severity of each child's symptoms.

Presently, little is known about the school settings of LKS children with central auditory processing disorders as opposed to those with sensorineural hearing losses in that children with LKS are very few in number. Our concern is that most teachers have no experience with such children. Whenever these children demonstrate to their teachers some recovery of their auditory verbal ability, auditory verbal training combined with sign language training should be initiated. In addition, transferring a child to a mainstream setting or providing education specializing in auditory verbal training should be considered. In Japan, schools providing educational classes for special needs children are placed into five categories: physically, intellectually, hearing, visually, and emotionally impaired. Though the recent trend is toward integrative education, even a token education, this trend is not only useless but it may be harmful. The findings from our Project B survey of the school settings of LKS children are shown in Table 5.2.

Amongst the younger children with LKS, the proportion of these children who were educated at a school for the intellectual disabled was high. When these children became older, an increased number of them had their educational setting changed to a hearing-impaired school. This was very important for them because LKS children usually have intact intellectual capacity. These children's academic progress and their interests in the outer world should be fully enhanced. Please reference patient I in the following section. A few of these children required various types of special education which was very useful regarding their long-term prognoses.

Table 5.2 Schools of LKS patients receiving/received education (Project B)

	Male	Female	Total
Elementary school			
Mainstream	17	10	27
Special needs class for children with intellectual disabilities	12	7	19
School for intellectually retarded children	2	1	3
Class for children with a hearing impairment	2	3	5
School for hearing impaired children	6	7	13
Others	0	0	0
Junior high school			
Mainstream	6	6	12
Special needs class for intellectual disabilities	4	3	7
Special needs school for intellectual disabilities	3	5	8
Special needs class for hearing impairment	2	3	5
Special needs school for hearing impairment	3	7	10
Others	0	0	0
High school			
Mainstream	3	5	8
Special class for intellectual disabilities	0	0	0
Special school for intellectual disabilities	1	1	2
Special class for hearing impairment	0	0	0
Special school for hearing impairment	1	4	5
Others	0	0	0
University, college, junior college	0	0	0
Vocational school	1	0	1

By the way, home training or education/rehabilitation/daily life at home from an early stage is important. Parents are no surprises shocked by their change of their children. However, to raise their children as a whole includes to nurture physical, psychological, emotional, social and intellectual development and to cultivate their ability depends on their children's states and disposition.

One of our patient's parent's efforts are shown in picture cards the father made for his daughter (Fig. 5.2).

Fig. 5.2 Daddy's handmade cards to try to make his daughter (patient D) to learn the Japanese language

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Chapter 6
Case Histories

In this section, the author presents and discusses 9 of her patients (A to I) with LKS and these patients taught us a lot about the important clinical manifestations of LKS. She ordered these patients by their ages of onset of LKS.

A brief clinical summary of each patient is shown in Table 6.1. The first part of each case history, very short summary about the typical features, and meaningful considerations which teach us about LKS are shown in the parenthesis.

6.1 Patient A: 4 Years Old, Female

[Over the course of 15 years this patient showed improvement in her clinically observed verbal and nonverbal abilities. Although she still had a lot of difficulty in her daily life, her own marvelous efforts and those of her family to overcome her disability had an obvious positive effect. When she was a toddler her SVR, MMN, and P300 to verbal and nonverbal stimuli were effective to objectively establish and quantify her hearing ability.]

At 4 years of age her chief complaints were loss of speech and periodic attacks of loss of consciousness. Family history was unremarkable. Her early motor and mental development was normal. She uttered her first meaningful word at 15 months of age and from thereon she steadily acquired vocabulary. She loved to sing and often sang along with animation.

Beginning at her age of 2 years 9 months she gradually lost her speech [aphasia]. An ABR taken at that time was normal. At her age of 3 years and a half she incurred a momentary epileptic seizure which induced an eyelid flutter followed by fever and clouded consciousness. Her EEG taken at that time revealed bilateral spikes and wave complexes over the mid temporo-posterior cortical areas.

When she was 4 years old, she began to suffer seizures about 5–6 times an hour. She was prescribed VPA and her seizures subsided. After this episode, her speech

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Table 6.1 Summary of clinical features of patients

Patient	A	B	C	D	E	F	G	H	I
Sex	F	F	M	F	M	M	M	M	F
Age at last seen	19y	10y	17y8m	57y	50y	15y	48y	10y	21y
Onset age	2y	2y8m	4y3m	4y7m	5y	5y3m	6y4m	6y7m	7y10m
Age at first visit	3y9m	4y4m	6y	5y	8y	14y10m	8y	8y	8y9m
Before the onset	No problem	No problem	No problem	No problem	No problem	No problem	No problem	No problem	Delay a little
Suspected disease	Hearing impairment	LKS	Heller disease	Brain tumor	Brain tumor, hearing impairment	Epilepsy	Hearing impairment	Rolandic epilepsy	LKS
Symptoms at onset	No speech, poor understanding of conversation, gesture poor response to sounds, normal ABR	Poor response to call, no speech, poor understanding to speech	Poor understanding of speech, musical instrument, and environmental sounds	Poor understanding of the other's speech, tone deaf response to others	Could not understand what his teacher said	Loss of speech at 5 y3m, dysarthria, seemingly hearing impaired	No response to call, ask back frequently, dysphasia, no speech	Generalized tonic convulsion	Perseveration of words, loss of words within 2 weeks
Epilepsy	cps	cps	Right hemiconvulsion	cps autonomic seizure	None	cps right hemiconvulsion	None	GTC	Drop attack
Remission and exacerbation	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive

Verbal symptoms	Verbal and nonverbal agnosia	Loss of meaningful words, frustrated in impaired	Sensory aphasia	Sensory aphasia to auditory agnosia	Sensory aphasia to auditory agnosia	Dysarthria, pronunciation like foreigners, seemingly hearing impaired, cannot stop speaking	Sensory aphasia to auditory agnosia	Dysphasia after epileptic seizure, then no spontaneous word	Perseveration of words, loss of speech within 2 weeks
Word deafness	–	+++	Sensory aphasia	–	Sensory aphasia to word deafness	+	+	–	–
Latest IQ	83(V68 P103)	DMT88	89 (V65 P116)	92 (V88, P102)	115 (V101 P132)	68 (V68 P75) Raven33/36	122 (V106 P132)	DMT89 (7y5m) 105 (V110, P99) (8y0m)	About 65–80
EEG in acute stage	Spike and waves in bilateral mid temporal to parietal	CP dominant sharp & slow in awake stage, right dominant frequent spike and waves in asleep	Frequent right temporal dominant spike and waves (C3 C4 T4)	rP to r posterior T dominant	F8 C3 P3 T3 spikes, spike and waves	Diagnosed as Lenox Gastaut syndrome	Spike and waves at T3	Rolandic spikes (normalized at 8 years old)	Diffuse spike and wave, multiple spikes
Pure tone audiometry at acute stage	Normal	30-40-dBby BOA	Normal	Almost normal	Normal	Mild depression at lower frequency	Normal	Normal	1k 80 dB at 8 years old, normalize at the age of 20 years

(continued)

Table 6.1 (continued)

Word discrimination test	Depressed	Could not be tested	Not known	Depressed	45% /50% (r/l) at 50dB at the age of 8 years old	Decreased hearing at increased sound pressure	Rt30%, lt 43% at 40dB, rt 57%, lt 71% at 50dB when 7 years 3 months	Decreased discriminability in increase sound pressure. Left ear dominant	Could not be tested
Musical ability	She loved to sing songs. She would not sing a song after the onset of the disease.	She loved to sing songs in exact way but did not sing after the onset of her disease, if she tried to sing, melodies and rhythms were messed.	He could not discriminate sounds of musical instruments.	She completely lost her musical ability.	He became off-tempo and became mistimed when playing piano. He said he became to play it again skillfully after he grew up to adult.	Before the onset of the disease, he was talkative and loved singing. He has not sung anymore after the onset of the disease. In his recovery phase, he again began to sing but he became tone-deaf. He could not play any musical instruments. Sound volume of TV became too loud.	He sang well before but he never sang any more.	He played piano and loved to play harmonica before the onset of the disease. As the first grader of an elementary school, he could not understand rhythm. He did not sing songs and play any instruments.	A record said that her humming was heard but not confirmed when she was 17 years old. She sings no songs at 20 years of age.

Abbreviation
LKS: Landau–Kleffner syndrome. Epilepsy: cps, complex partial seizure; r, right; l, left. IQ V: VIQ, verbal intelligent quotient; P: PIQ, performance intelligent quotient. Audiometry: BOA, behavioral audiometry. IQ test: DMT, draw a man test; Raven, Raven colored Matrix test. EEG: C, central; P, parietal; T, temporal.

nevertheless deteriorated. She began to utter only meaningless sounds. She was then diagnosed with early-onset LKS. Her visual cognition was very good and she used gestures copiously. She could construct a toy house with blocks [no construction apraxia]. Her receptive language was better than expressive language [motor aphasia]. She fell into a panic when she could not make others understand her. She could perceive the telephone ringing, knocking at the door banging and the crumpling of paper. However, she could not discern speech if the person stood behind her and the speaker had to tap her on the shoulder to get her attention.

Methylprednisolone pulse therapy ameliorated her EEG but incompletely improved her auditory and verbal symptoms (Fig. 5.1 in the Sect. 5.1). Subsequent to her pulse therapy she took prednisolone, VPA, CZP, and CLB.

Her EEGs, SVRs, and MMNs were regularly evaluated using paired verbal ([a]and [æ]) and nonverbal stimuli (1 and 2 kHz tone bursts) because at an earlier age she was too young and her symptoms were too severe to evaluate her condition subjectively. We decided her to evaluate her cognitive ability of verbal sounds objectively using ERPs. When her EEG abnormalities were severe, her auditory symptoms, abnormalities of SVR and MMN, increased. The significant findings from these evaluations were that the N1s of her SVRs provoked by tone bursts improved prior to those provoked by verbal sounds. On the other hand, as her verbal symptoms improved the N1s of her SVRs to verbal stimuli became worse prior to those provoked by tone bursts. When her EEGs improved her clinical and physiological test results also improved (Fig. 3.21 in the Sect. 3.4.2).

When she first came to see us, her SVR to nonverbal stimuli could not be recorded. However, during her recovery phase, the SVR N1 response to nonverbal sounds could be provoked followed, over time, to the appearance of N1 to verbal stimuli. These SVR findings aided us in confirming the actual recovery progress of this patient who could not otherwise be evaluated by a voluntary means.

In spite of her LKS symptoms, her overall intelligence remained normal and her IQ, on the Draw a Man test at age 4 was 100.

At her age of 8 years, her epilepsy was controlled and her EEGs normalized. At 9 years of age, antiepileptics were discontinued.

She had been educated, from the age of 9, at a special need school for the hearing impaired. She acquired vocabulary and could read script when presented by animation. She was healthy and excelled at sports. At 13 years of age she could understand most of what she was told but she still had difficulty in acquiring new vocabulary and in learning new Kanji (Chinese ideographs used in Japanese writing). Her vocabulary remained limited. She displayed an elective mutism that is, she spoke in halted Japanese at home but did not speak outside of her home. She was good at arithmetic and mathematics. Her Raven colored matrix scores were 35 correct responses out of 36 trials which indicated that her visual reasoning was essentially perfect. Her Peabody Picture Vocabulary test indicated that her vocabulary level was between 6 years and 10 months to 12 years. Her WISC III evaluation revealed that her VIQ, PIQ, and FIQ scores were 68, 103, and 83, respectively.

At 15 years of age her pure tone audiometric findings were normal but she scored low on word discrimination testing. Her ABR was normal.

She enjoyed her time at the special needs high school for the hearing impaired, studying hard at school and becoming an excellent athlete. She began to speak outside of her home by whispering. It was difficult for her to understand melody and rhythm despite much effort. She did not sing since the onset of her LKS disorder. She graduated from high school and began to study business affairs in a college.

6.2 Patient B: 4 Years Old, Female

[This patient is on a trend toward a favorable recovery despite the young age of onset of her disease]

When we first met her, she was 4 years 5 months old when she had her initial encounter with us. Her chief complaint was loss of speech and her difficulty in understanding conversation [aphasia]. Her mental and motor development was normal until her age of 2 years and 8 months. She had enjoyed singing to animation songs but as she gradually lost her speech and singing. She was brought to a children's hospital. On intake, an EEG revealed continuous diffuse high voltage spikes and slow waves which were dominant over the right hemisphere. LKS was diagnosed and Levetiracetam (LEV) and Zonisamide (ZSM) were prescribed. Methyl predonisolone pulse therapy made her EEG remarkably improved. However, her clinical auditory verbal symptoms were not resolved. She was then enrolled in a special needs elementary school for the hearing disabled. She gradually acquired an ability in auditory verbal communication. As her third grader, she moved to the mainstream. Because her verbal ability has steadily improved and her former classmates with hearing impairment rarely could use oral communication. Her vocabulary and her desire to oral communication with others were slowly but steadily improving. As of yet, she still does not sing songs. She has had no epileptic seizures for many years. Her subsequent EEGs have improved with no detectable spikes on the recordings. She is now 10 years old and she enjoys school life with her friends who accept her handicap in pronunciation and her marginal vocabulary. Her hearing remains poor but it is steadily improving.

6.3 Patient C: 6 Years Old, Male

[He recovered from his auditory verbal ability with the least sequela. He became a quality student at high school in mathematics but Japanese and English were difficult subjects for him. He was continuing to lose his musical abilities at his last visit when he was 17 years old**.]**

His chief complaint at 6 years of age was deterioration in auditory comprehension and loss of speech.

His motor and mental development was normal until he was 4 years old, when he gradually lost to comprehend what was said to him. Prior to the onset of his disease

he often sang nursery rhymes and had an interest in the sounds of musical instruments.

He then began to speak less and less but he was euphoric and had no concern about his condition [anosognosia]. He became hyperkinetic. He began to misspell words [dysgraphia] even his own name in Hiragana (Japanese phonetic letters originated and changed from Chinese letters). Five months later he responded only to his name. He could not differentiate human voices and environmental sounds [auditory agnosia]. He had right hemi-convulsions for a brief time. At a university hospital he had an EEG which showed frequent right temporal dominant spikes. At that time, it was suspected that he had Hellers' disease. Just before 6 years of age it became, he became impossible to draw pictures [construction apraxia] or to play by himself or with his friends.

At 6 years of age he could not understand anything what was said to him [sensory aphasia] and most of what he said to other people was unintelligible [dysphasia]. He could not imitate another persons' motions nor could he understand the meaning of gestures [apraxia and visual agnosia]. His voice became louder as if he could not hear himself [seemingly hearing impairment, cortical deafness?]. Five months later, he did not respond and understand any environmental sounds [nonverbal auditory agnosia] including musical instruments and human voice [verbal and nonverbal auditory agnosia].

At 6 years and 6 months of age, he began to understand the meaning of gestures. Another EEG at a university hospital was abnormal with spikes and slow waves with left frontal and occipital dominancy. The slow vertex potential was reported to be normal. His auditory verbal comprehension gradually improved and his speech returned to normal. During this recovery phase he became temporarily depressed [possibly due to a psychological reaction].

He was treated with anticonvulsants (PB, CBZ, and VPA) and the drug was tapered with no recurrence of his seizures. During his disease process he was moved from a mainstream school setting to a special needs class for the intellectually impaired. Upon entering high school he was returned to a mainstream school. He had no trouble at home nor at school. He was smart and good at mathematics but poor at Japanese and English at high school.

6.4 Patient D: 5 Years Old, Female

[This patient has been followed for more than 50 years. She had a severe sequela of auditory agnosia despite vigorous long-term training and positive behavior]

Her initial complaints, at 4 years and 7 months of age, were deterioration of verbal comprehension, dysphasia, and loss of speech. Her early development was completely normal. She spoke well and sang nicely. She gradually lost her comprehension of speech and showed inappropriate responses to verbal commands followed by severely distorted speech [dysphasia]. She talked a lot but her speech was mostly jargon [sensory aphasia]. When asked to bring matches she would bring an ashtray.

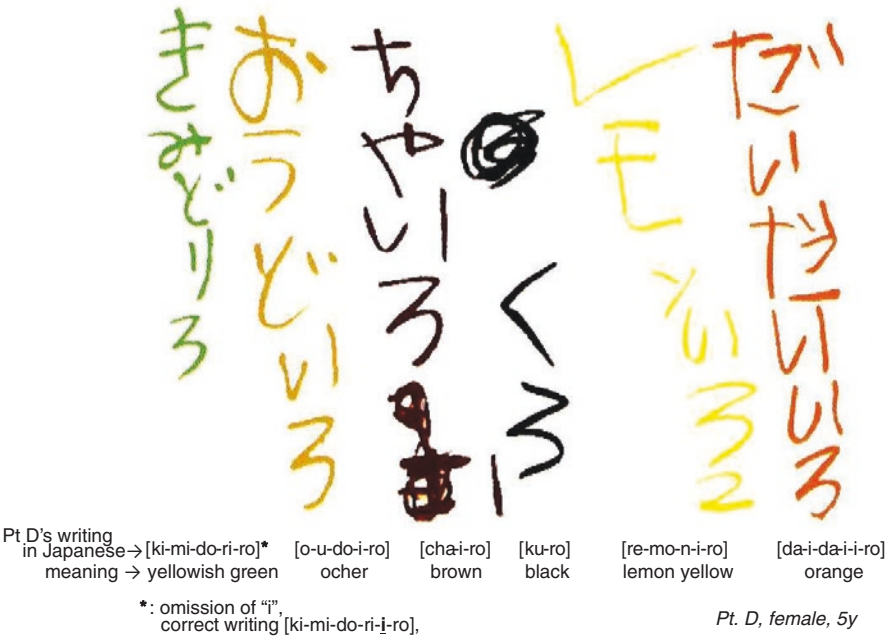

Fig. 6.1 Patient D's writing, 5 years old, female. When she wrote these letters, she could not speak and could not understand words and conversation. However, this writing shows she could fully understand the name and meaning of colors

She said "koori" (ice in Japanese) instead of cocoa [diverted language]. Two months later she incurred complex partial seizures. These seizures were easily controlled by DPH and PB. However, over the next few months her language disorder progressed to total aphasia. She remained euphoric and did not care about her handicap [anosognosia]. By the time that she reached the age of 5 years she was totally aphasic. Her first admission to a university hospital was at her age of 5 years and 2 months. She had almost completely stopped speaking and could not follow any verbal commands. She could understand her situation with the aid of gestures. She could discriminate between colors despite her inability to name them (Fig. 6.1). Her auditory response was unstable but she could localize sounds [residual sound lateralization ability]. Her mother began to teach her Hiragana (Japanese phonetic letters) and she tried to teach her daughter as much vocabulary as she could. She could not verbalize words or sentences but she could copy letters.

Her father made many picture cards and taught her Japanese words and phrases. She did reasonably well at drawing pictures. She could not comprehend the rhythms or melodies of her formerly favorite songs [amusia]. She gradually improved because of vigorous speech therapy and education at a school for hearing-impaired children along with her parents' contribution.

She entered and graduated from a mainstream high school. She then attended a job training school and was subsequently hired by a company as an office worker and continues to work there. She is a very sincere person and she has continued to make efforts to increase her vocabulary.

After 50 years of follow-up, she is talkative well with loud voice. Her unusual pronunciation and intonation are unusual. She still has difficulty talking on the phone and in participating in meetings. She needs a sign language interpreter. She still cannot discriminate various rhythms and melodies and she cannot appreciate any music nor the sounds of musical instruments [amusia-auditory agnosia]. Her writing ability remains almost normal with some incorrect grammar. She complains that other kind of people talk to her in a loud voice because they misunderstood that her hearing is impaired. Nevertheless, she remains active and she makes every effort to increase her vocabulary and to live an involved life with her family.

6.5 Patient E: 8 Years Old, Male

[He has been followed up for many years and confirmed his complete recovery from LKS. We documented a stage of auditory verbal agnosia and pure word deafness which was followed by reactive depressive period for several weeks.]

Our first encounter with him was when he was 8 years old. His chief complaint at that time was a deterioration in auditory comprehension and dysphasia began when he was 5 years old. His mental and motor development was normal prior to the onset of his disease. At 5 years of age, his kindergarten teacher told his parents that he could not understand what he was said to him [auditory verbal agnosia]. An abnormal epileptiform EEG was obtained and he was put on anticonvulsants. By his age of 7 years, he could not understand nor repeat words said to him. His articulation was inadequate. At 7 years and 2 months of age, he complained of impaired auditory comprehension by himself. He spoke slowly and vaguely and his speech was almost incomprehensible. When admitted to a university hospital at 7 years and 4 months, he was friendly and unconcerned about his disabilities [euphoria, anosognosia]. He had essentially no auditory comprehension and he could not differentiate between male and female voices. However, he could appreciate other daily environmental sounds. He communicated by writing and by gestures. His speech was slurred and monotonous, he displayed logorrhea and he had difficulty with word-finding. His pronunciation was distorted and his use of grammar was incorrect. He played piano out of tempo with loss of rhythm and harmony (auditory agnosia and amusia). Three such episodes of auditory agnosia occurred at 6-month intervals. His condition recovered and exacerbated a few times over the next few years. During his remissions he became depressed about his handicaps but he eventually completely recovered, graduating from a good private university and entering the business field. He is now over 40 years old. He no longer has complaints of auditory verbal problems. He says that he now plays piano skillfully.

6.6 Patient F: 14 Years Old, Male

[This patient inspired us to explore the relationship between LKS and autistic disorders.**]**

Before the onset of his disease at 5 years old, his mother did not recognize any atypical development nor abnormal behaviors in him. He spoke fluently and sang songs skillfully. When he was 5 years and 3 months old, he began to speak less and less and his speech became distorted. He said [taion] instead of lion ([laion]) and [ariueo] instead of [aiueo] (Japanese vowels)]. An otolaryngologist found nothing wrong in his hearing. When he was 6 years old, he often became absent-minded and seemed to be hard of hearing. At 6 years and 5 months of age, he had an epileptic seizure during sleep. Following this episode, he had several more epileptic attacks consisting of clonic convulsions of his right arm and generalized tonic–clonic convulsions. When spoken to him in a loud voice, he responded. He was able to write messages to communicate with others. He spoke a few words with distorted sounds. His EEG was highly abnormal with continuous spikes and waves (it was evaluated as CSWS). ABR was normal. He began to take VPA. His school results continued to decline and he moved from a mainstream to a special class for the intellectually impaired. At that time, he could only respond to loud voices [auditory agnosia] but he could communicate by writing. The words which he uttered were distorted and then he became totally speechless [aphasic]. Three times steroid pulse therapy at a university hospital was effective in normalizing his EEG. His epileptic attack ceased when he was 10 years old. CSWS on his EEG improved following administration of CZP and VPA. When he was 10 years old, his full IQ was reported as 75. Draw a Man test indicated that his IQ was 50 [agnosia of physical image of his body. Because formerly he was a typically developed boy, lowered IQ suggests the disease made him significant damage in his cognitive ability.] Intertictal SPECT scan was reported as the presence of hypoperfusion of the left anterior inferior temporal lobe. Spike discharges over the right temporal lobe were noted by MEG.

His hearing gradually improved in time but it remained to be difficult for him to understand complex sentences. His pronunciation continued to be very poor with a lot of jargon.

He was referred to us for further evaluation because of his diagnosis of LKS. He was 14 years old at that time and his conversation and his behavior were typical of an autistic child. Eye contact was poor and he talked continuously, usually repeating the same topic in a monotonous manner and with a loud voice. His speech was limited and intemperate when asked about a certain animation character. Interactive communication was difficult for him and he could not tolerate disruptions in his routine activities. His drawings consisted of the same robot-like character which always had the same pattern. At home, he watched TV set at maximum volume. Since his disease onset he never sang and was very poor at playing a musical instrument. However, just before his last visit at age 14 he began to sing once again. However, his songs are completely out of tempo with poor melody and rhythm.

Retrospectively examined at 15 years old, his PARS (pervasive developmental disorders) scores on the Japanese Autism Society Rating Scale were 7 at the onset of LKS around 5 years old (less than 8 indicates that the patient is unlikely to be autistic) and 23 at 15 years old (more than 20 points strongly suggests that the patient is autistic). Both scores seem to suggest that the patient had ASD-like symptoms after (or as a sequel) of his disease onset.

On a psychological test at our clinic, the Raven Colored Matrix test, scored 33 of 36 which was very good at his age. After intensive treatment and speech therapy his PIQ was 83 but his VIQ and full IQ could not be evaluated. DMT evaluation indicated that his IQ as 75. His ABR, VEP, and SSEP were all normal.

His clinical course suggested to us that his autistic behavior seemed to be a sequela of his LKS which indicates to us that some autistic patients may have common brain lesions or common neural network disruptions.

6.7 Patient G: 8 Years Old, Male

[This patient presented with the typical clinical stages of exacerbation and remission followed by complete recovery. His writing disclosed how this patient with auditory agnosia perceived verbal sounds.**]**

His early development was completely normal. At 6 years and 4 months of age, his chief complaint was that he ignored other peoples' voices. He had to ask back frequently to what he was said to [auditory verbal agnosia], dysphasia, and loss of speech [aphasia]. He became to ignore when other people called him [verbal auditory agnosia]. These symptoms subsided within a month.

At 7 years of age, the same symptoms recurred. He began to ask that speech directed to him to be repeated. He started to talk less and less. He became restless and hyperkinetic [auditory verbal agnosia and hyperkinesia]. He was diagnosed as hearing impairment of central origin. He was admitted to a university hospital when he was 7 years and 8 months old. On admission, he was euphoric and anosognosia was evident. He was clumsy and could understand only simple verbal commands. He showed logorrhea with many errors in pronunciation and incorrect grammar. His intonations were unusual. When he read a book out loud he made many errors (omissions and substitutions) and he could not understand the contents which he read. His writing suggested an impairment of auditory recognition. He made many mathematical errors (inattention or acalculia) but he could accurately copy letters and pictures. His auditory memory span was diminished. Right versus left discrimination and finger recognition were inaccurate [Guerstman-like syndrome phenomenon]. Apraxia could not be confirmed. Of course, these might be due to inattention or cognitive deficit.

An EEG showed a marked abnormality typical of LKS; significant epileptic activity which increased during sleep. His pure tone audiogram, ABR, and SVR were normal. His word discrimination test scores indicated an impairment of his speech perception. However, he could discriminate between various nonverbal

environmental sounds. Over many years, these symptoms remitted and exacerbated. During remissions he could communicate by gestures and by writing letters and sentences (mild word deafness). In time, his language and hearing disorders gradually improved. He is now older than 50 years old and works as a capable businessman. He has no current complaints regarding his previous auditory and verbal symptoms.

6.8 Patient H: 8 Years Old, Male

[He was diagnosed as Rolandic epilepsy before the final diagnosis of a relatively mild LKS at a university hospital. He inspired us to explore the relationship between LKS and Rolandic epilepsy.]

His development was normal until the onset of his disease at the age of six. He made a speech to a big audience when he was 5 years old. When he was 6 years 8 months of age he had an early morning generalized tonic–clonic convulsion which lasted for 2 min. An EEG revealed Rolandic spikes and he was diagnosed with benign Rolandic epilepsy. After this episode, he subsequently had four more seizures and he was put on VPA and then CLB. His Rolandic epileptic activity resolved soon and he became seizure-free. One year later he began to make vocalization errors such as saying [akinomenai] instead of [akiramenai] ("akiramenai" means "never give up" in Japanese). Then it became difficult for him to understand other people's speech. He was diagnosed as LKS at a university hospital. His auditory verbal symptoms remitted a few times. Oral DZP taken at bedtime relieved his symptoms slightly. He took ESM and became seizure-free but he continued to have incorrect pronunciation and to utter ambiguous sounds.

His ability to read out loud at school declined. It was difficult for him to discriminate word sounds. He could discriminate environmental sounds. He was formerly good at sports but he became clumsy. Before the onset of the disease, he loved to sing and to play harmonica but he developed tone-deafness making it difficult for him to regulate his vocalization intensity/melody and he could no longer play the harmonica.

At 7 years of age, his verbal IQ was 86 which, at the age of 8, increased to 110 afterward. Epileptic seizures were controlled by medication. He continued to misperceive words such as [shinkansei] instead of [shinkansen ("bullet train" in Japanese)]. Over the next 3 years, he has recovered slowly but steadily. When he was 9 years old his SPECT was reported to reveal a mild reduction of blood flow in the left temporal and hippocampal gyri.

He is active and has no concerns about his state (anosognosia). His previous disabilities in school and social life are no longer problematic for him. His paroxysmal EEG activity has decreased over the years. He is an intelligent boy and he has little difficulty in comprehending conversation.

6.9 Patient I: 10 Years Old, Female

[She informs us at to the difficulty in choosing the most appropriate educational setting for LKS patients.]

She was born full term without any concern of her physical and mental development until the disease onset. As the first grader of an elementary school, she acquired grade-level skills in reading and writing. However, at 7 years of age, her speech degraded to the point where she could only utter limited sounds. Within 2 weeks she stopped speaking entirely and it became difficult for her to understand any conversation. Upon hospitalization at a center hospital in the district, EEG abnormalities (diffuse 3 Hz spike and waves and multifocal independent spikes with exacerbation during sleep) were observed and VPA was administered. Two months following hospitalization she had a drop attack and loss of consciousness. Even after three rounds of steroid pulse therapy she still could not utter a word irrespective of improvement of her EEG findings. Her visual recognition was normal and she could read simple words. She could write her name but did not understand what she wrote. ZSM, CZP, and ESM were administered subsequently to VPA. These medications were ineffective and caused drowsiness. She remained active with inattention and she behaved too gaily. Speech therapy was also attempted concurrent with these medications.

At a university hospital, PET and MEG scans were taken. The PET scan indicated a decrease in the uptake of ^{18}F-FDG in the right frontal to temporal lobe, especially the posterior temporal lobe. Right then to left temporo-parieto-occipital equivalent current dipoles of spikes and wave complexes were confirmed by MEG.

She went back to school but could not comprehend what was being taught. She became inattentive and showed few facial expressions. A second round of steroid pulse therapy was a bit more effective. She regained her facial expressions although she still could not utter a word. She could read simple words and write her own name but could not comprehend what she wrote. She could auditorily perceive finger rubbing sounds next to her ear and the sounds of a train [normal hearing acuity]. She was euphoric as regards her disabilities [anosognosia].

She tried to communicate with gestures. She could say a few words which were generally understandable. Her Raven Colored Matrix test score was 16/36. She was affectionate toward her mother and she was enrolled in a special needs junior high school for the hearing impaired. However, she had almost no capacity for oral communication and she was subsequently transferred to a special needs high school for the intellectually impaired from which she graduated. Although her auditory verbal understanding improved, she still uttered only mimetic word which actually had no meaning.

After graduation from high school at 18 years of age, she started to work at a commuting welfare workshop. She is pleased to be able to make and wrap articles for daily use. She once tried the Makaton visual communication method because of good ability in visual cognitive ability *in elementary to junior high school*, but has

not used it since. Even though she could read and write Kana (Japanese syllabary characters) during her school days, she has since declined any kind of classwork. She does not use sign language. She understands simple conversations but she never speaks on a voluntary bases.

When she was 20 years old, she again visited our clinic seeking information regarding her prognosis. At that time she seemed to sufficiently understand her situation and she even tested her clinicians to see if they could understand her sign language or fingerspelling which she had learned in the past. To date, she seems to be satisfied with her daily routines but she is totally dependent on her mother for everything at home. Hence, her mother was quite surprised by her daughters' voluntary cooperation with our tests such as audiometry, ERPs, MRIs, and MEGs.

Our immediate emphasis is to persuade her to relearn how to communicate with others. Her pure tone audiometry and otoacoustic emissions remain normal. She still cannot differentiate between various environmental sounds even when presented concurrently with a visual representation. Click-evoked ABRs showed a prolonged wave I measurement (2 ms presented at 70 dB SPL) but her thresholds were normal.

Her MEG indicated normal field mismatches using different tone durations, two different tone burst frequencies, and two types of verbal stimuli and that her ERPs could be evoked. These results were very good as compared to other LKS patients. The patient's mother believes her daughter's potential abilities could exceed what she had originally thought to be possible.

When she was enrolled at a special needs junior high school for the hearing impaired, her verbal skills began to improve. Unfortunately, she was provided with almost no training in oral communication and insufficient training in visual communication. Subsequent enrollment in a special needs school for the intellectually impaired proved to be comfortable setting for her but she could not fully exercise her mental abilities. As illustrated by this patient, it is very difficult to select the most appropriate educational setting for LKS patients.

Chapter 7
Fifty Years in the History of Landau–Kleffner Syndrome (LKS)

To celebrate the 50th year since the publication of the seminal LKS paper by Drs. Landau and Kleffner, a small conference, "Fifty Years of Landau–Kleffner Syndrome International Symposium: A Tribute to William Landau and Frank Kleffner", was held on November 1–3, 2007 at a beautiful castle located in the small village Biesen in Belgium. This castle was built in the sixteenth century and named the Alden Biesen (Fig. 7.1) which means old Biesen. It was surrounded by beautiful flowering gardens and it had a classical and cozy atmosphere. Approximately 150 individuals, from many countries, attended this meeting. I was honored to be the only Japanese participant. The organizing committee included Drs. Arts WF, Wijingaert LD, Marquet P, Paquiert PF, and Van Bogaert P. This symposium was held under the official auspices of the International League Against Epilepsy *(ILAE)*.

Drs. Landau and Kleffner were the special guests at this meeting and they also made a presentation during the symposium. Proceedings of this symposium were subsequently published in Epilepsia 50, supplement 7, August 2009. It was a lovely and memorable conference devoted to the history of LKS. The program is presented in Fig. 7.2.

Fig. 7.1 The Alden Biesen, Biesen, Belgium

M. Kaga, K. Kaga, *Landau-Kleffner Syndrome and Central Auditory Disorders in Children*, Modern Otology and Neurotology,
https://doi.org/10.1007/978-981-10-1479-6_7

Friday 02 November 2007

8:20-8:30 Organizing committee: welcome

8:30-10:30 Historical perspectives

Chairs P.F. Paquier (Belgium) and E. De Wijngaert (Belgium)

08:30-09:00 W. Landau and F. Kleffner (United States)
The Landau-Kleffner syndrome

09:00-09:30 C.A. Tassinari (Italy)
Electrical status epilepticus during slow sleep : "The Penelope syndrome"

09:30-10:00 N. Fejerman (Argentina)
Atypical rolandic epilepsy

10:00-10:30 P. Plouin (France)
The EEG phenomenon of continuous spike-waves during sleep

10:30-11:00 Coffee break

11:00-13:00 EEG aspects of the syndromes with CSWS

Chairs M. Bureau (France) and P. Plouin (France)

11:00-11:30 M. Scheltens de Boer (The Netherlands)
Guidelines for EEG analysis

11:30-12:00 Discussion : M. Bureau (France)

12:00-12:30 R. Guerrini (Italy)
Idiopathic and symptomatic forms

12:30-13:00 Discussion : P. Plouin (France)

13:00-14:00 Lunch

14:00-16:00 Clinical aspects of the syndromes with CSWS

Chairs O. Dulac (France) and G. Gobbi (Italy)

14:00-14:30 R. Tuchman (United States)
CSWS-related autistic regression versus autistic regression without CSWS

14:30-15:00 C. Seegmuller (France)
ADHD versus frontal epileptic disorder with CSWS

15:00-15:30 C. Billard (France)
Specific language impairment versus Lnadau-Kleffner syndrome

15:30-16:00 General discussion

16:00-16:30 Coffee break

16:30-18:30 Atypical observations

Chairs E. Roulet-Parez (Switzerland) and N. Fejerman (Argentina)

16:30-17:00 E. Hirsch (France)
Famillal observation : Insight Into possible genetic factors

17:00-17:30 P. Veggiotti (Italy)
CSWS without neuropsychological deficits

17:30-18:00 C.Bulteau (France)
Acquired cognitive dysfunction without CSWS

18:00-18:30 P. Paquier (Belgium)
Acquired cognitive dysfunction with focal sleep spiking activity

Fig. 7.2 Program of "Fifty Years of Landau–Kleffner Syndrome International Symposium: A Tribute to William Landau and Frank Kleffner" (from http://www.lks-symposium.eu/program.htm, inaccessible now)

Saturdy 03 November 2007

8:30-10:30 Patho-physiology

Chairs C.A. Tassinari (Italy) and E. Hirsch (France)

08:30-09:00 S. Seri (United Kingdom)

Neurophysiology of CSWS-associated cognitive dysfunction

09:00-09:30 S. Moshe (United States)

The epileptic hypothesis : developmentally retated arguments based on animal models

09:30-10:00 P. Maquet (Belgium)

Influence of sleep on cognition

10:00-10:30 General discussion

10:30:-11:00 Coffee break

11:00-13:00 The contribution of new investigation technologies

Chairs P. Van Bogaert (Belgium) and R. Guerrini (Italy)

11:00-11:30 X. De Tiège (Belgium)

FDG-PET and EEG-fMRI

11:30-12:00 R. paetau (Finland)

Magneto-encephalography

12:00-12:30 C. Stam (The Netherlands)

Nonlinear EEG analysis

12:30-13:00 General discussion

13:00-14:00 Lunch

14:00-15:30 Contemporary therapies

Chairs K. van Rijckevorsel (Belgium) and S. Moshe (United States)

14:00-14:30 W.F. Arts (The Netherlands)

Immuno-suppressant therapies

14:30-15:00 L. Lagae (Belgium)

New molecules and ketogenic diet

15:00-15:30 H. Cross (United Kingdom)

Surgical approaches

Fig. 7.2 (continued)

Saturdy 03 November 2007

15:30-16:00 Coffee break

16:00-18:30 Treatment : decision-making tree

Chairs W.F. Arts (The Netherlands) and H. Cross (United Kingdom)

16:00-16:30 M. Buzatu (Belgium) and O.Dulac (France)

The Paris experience with use of hydrocortisone

16:30-17:00 S. Shinnar (United States)

The New York experience with ACTH

17:00-17:30 G. Gobbi (Italy)

The Bologna experience without use of corticosteroids

17:30-18:00 H. Stroink and H.R. Van Dongen (The Netherlands)

The Rotterdam-Tilburg experienece of treatment of Landau-kleffner syndrome

18:00-18:30 General discussion

Sunday 04 November 2007

8:30-10:30 Rehabilltation and long-term outcome

Chairs H. Szliwowski (Belgium) and P. Casaer (Belgium)

08:30-09:00 M.N. Metz-Lutz (France)

The assessment of auditory function in CSWS, lessons from long-term follow-up

09:00-09:30 E. Roulet-Perez (Switzerland)

Sign language In Landau-Kleffner syndrome

09:30-10:00 pending: Long-term outcome

10:30-11:00 Coffee break

11:00-12:30 Symposium synthesis and closing session

11:00-12:00 T. Deonna (Switzerland): Synthesis and perspectives

12:00-12:30 W. Landau and F. Kleffner (United States): closing remarks

Fig. 7.2 (continued)

Part II
Related Central Auditory Disorders

Chapter 8
Adrenoleukodystrophy (ALD)

Abstract X-linked adrenoleukodystrophy (ALD) especially in childhood cerebral type is a metabolic degenerative disease with a severe clinical course of progressive deterioration until death involving progressive demyelination of the central nervous system caused by a defect in the *ABCD1* gene at Xq28.

The frequency of hearing impairment has been reported in a rather high percentage of the patients but the other apparent deteriorating motor, mental, and visual symptoms are often concealed. Thus central auditory dysfunction is not fully recognized and it is difficult to support patients directly for their difficulties from their handicaps. These symptoms are due to the localized brain lesions but because of the character of disease, the lesions continuously and progressively expanded to the whole white matter of the brain without treatment.

The duration of apparent hearing impairment continued not so long in their natural history. Serial change could be evaluated clinically, nerophysiologically, and neurophysiologically.

There are some types of leukodystrophy but they usually progress rapidly in the brain and the lesion expansion is almost uniform. Therefore, it seems difficult to recognize symptoms based only on the localized brain lesions. Even during the clinical evaluation of an ALD patient, such symptoms may often be overlooked.

Keywords Adrenoleukodystrophy · Auditory agnosia · Neuropsychological assessment · Neurophysiological examination

8.1 Etiology and Clinical Course of the Disease

X-linked adrenoleukodystrophy (ALD) is a metabolic degenerative disease with a severe clinical course of progressive deterioration until death involving progressive demyelination of the central nervous system, adrenal dysfunction, and

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accumulation of saturated very long-chain fatty acids (VLCFA) in various tissues and body fluids. It is caused by a defect in the *ABCD1* gene at Xq28 which encodes for a peroxisomal membrane protein (Mosser et al. 1993).

8.2 Clinical Types of ALD and Their Signs and Symptoms

There are several clinical phenotypes which are usually classified as childhood cerebral type (CCALD), adolescent cerebral type (AdolCALD), adult cerebral type (ACALD), adrenomyeloneuropathy (AMN), cerebello-brainstem type (CB-BS ALD), Addison type (ALD with Addison disease), preclinical male patients (PCM), and females with apparent symptoms.

Two cerebral types of ALD (CCALD and AdolCALD) may often initially present with gait disturbances, strabismus, abnormal vision, visual dysfunction, and intellectual and/or behavioral changes around 6–10 years old.

The prognosis of CCALD is very poor and patients usually pass away within a few years after their clinical onset followed by their deterioration of their physical and intellectual abilities (Suzuki et al. 2005). The prognosis of patients with AdolCALD is somewhat better.

The survey of hospitalized patients by Suzuki et al. gave light to the natural history of ALD: the initial symptoms of childhood cerebral-type ALD were intellectual deterioration 16/46, visual signs/symptoms 11/46, gait disturbance 4/46, psychic symptoms 4/46 and hearing disorder 3/46, and adrenal insufficiency 1/46 (Suzuki et al. 2005) (Table 8.1).

Tanaka et al. also examined the initial symptoms of their ALD. They reported that hearing problems presented as the initial symptom of their patients was noted in 13% of ALD patients (Tanaka et al. 1989) (Table 8.2).

Thus, hearing problems were not a rare finding and this should be importantly considered in the diagnosis of ALD. Usually, patients' intellectual deterioration, gait disturbance, and visual impairment are more easily detected by their family members and teachers than are their hearing disorder.

The Kaplan–Meier neurological progression evaluation in patients with ALD informs us that patients with CCALD are not symptom-free after following 1.3 years after their diagnoses of ALD and even patients with AMN show a gait disturbance within 4–5 months after their diagnosis (Suzuki et al. 2005) (Fig. 8.1).

Table 8.1 Initial symptoms of ALD (Suzuki et al. 2005)

Phenotype	The number of patients	Initial symptoms (*n*)							
		Intellectual	Psychic	Visual	Hearing	Gait	Sensory	Bladder	Adrenal
Childhood	46	16	4	11	3	4	–	–	1
Adolescent	14	2	2	5	1	4	1	–	1
AMN	39	–	–	–	–	37	3	1	–
Adult cerebral	33	5	19	3	1	11	1	2	1
OPC	13	1	–	–	–	9	1	–	2
Total	145	24	25	19	5	65	6	3	5

AMN adrenomyeloneuropathy, *OPC* olivo-ponto-cerebellar form

Table 8.2 Initial symptoms of 38 patients with ALD

Symptom	The number of patients	%
Gait disturbance	8	21
Visual disturbance	7	18
Psychiatric symptoms	6	16
Hearing disturbance	5	13
Convulsion	4	11
Poor writing	3	8
Intellectual deterioration	1	2.6
Delinquency	1	2.6
Dysarthria	1	2.6
Headache	1	2.6
Hyperpigmentation	1	2.6
Total	38	

Tanaka et al. (1989)

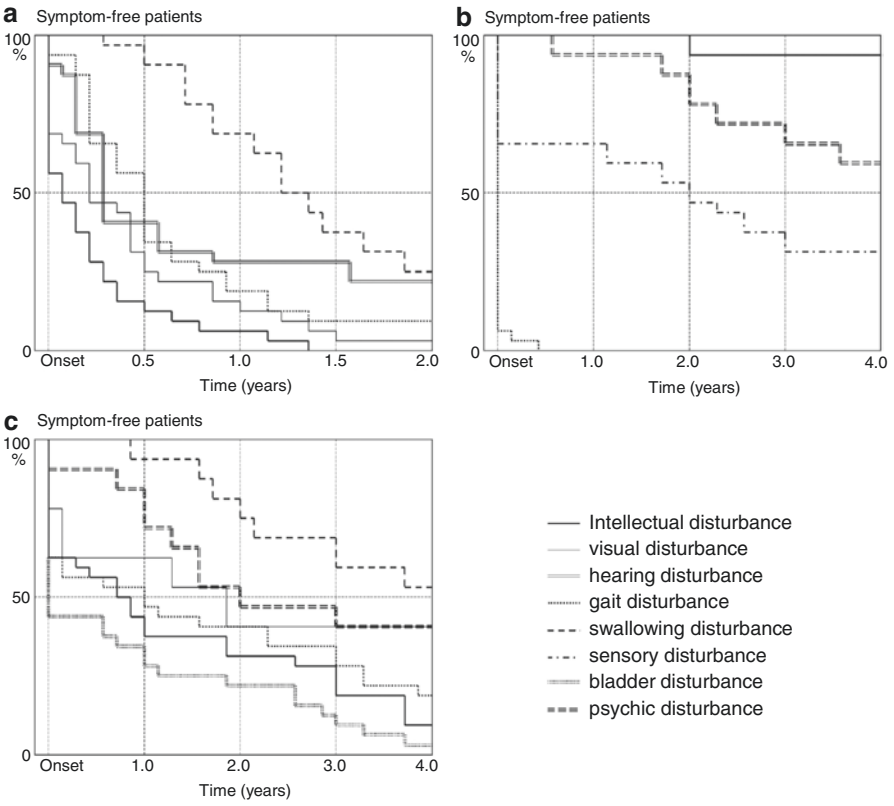

Fig. 8.1 Kaplan–Meier plot of neurological progression in patients with ALD (Suzuki et al. 2005). (**a**) Childhood cerebral form, (**b**) adrenomyeloneuropathy, (**c**) adult cerebral form. Vertical line shows the ratio of patients with no clinical symptom, horizontal line shows time course (years)

8.3 Diagnosis of ALD

The diagnosis of ALD is made by the observation of clinical signs, the determination of each patient's symptoms, and by special testing such as MRI findings and the finding of a high concentration of very long-chain fatty acid (VLCFA) in the serum. A definitive diagnosis nowadays hinges on the confirmation of the disease from a gene mutation in the *ABCD1* gene. However, it is impossible to differentiate the various clinical manifestations of the disease from the gene mutation itself or from the clinical types of the patients' relatives, even those who are their siblings. Clinically, presence of certain symptoms and confirmation of MRI lesions are the best way to diagnose ALD. However, neuropsychological/cognitive symptoms might be present before the appearance of MRI lesions (Furushima et al. 2009; Kaga et al. 2009). The introduction of ALD as part of the neonatal screening (Vogel et al. 2015) is a recent trend in several states in the USA and some European countries. This trend will ultimately positively impact the clinical care of ALD patients before the emergence of their clinical manifestations of the disease. On another front, such patients and their parents will no longer spend peaceful lives, but they will also have agonizing length of time which will continue as long as 5–50 years before having a specific diagnosis.

8.4 Hearing Impairment in ALD

Hearing impairment in ALD is primarily of central origin and is not due to an inner ear or cochlear lesion. In other words, the etiology of hearing impairment in ALD arises from white matter lesions in the auditory pathway. Of course, some patients have co-existing conductive hearing impairment due to otitis media. Hearing impairment has been found to the initial symptom of ALD (Tanaka et al. 1989; Suzuki et al. 2005) (Tables 8.1 and 8.2) but the actual details of the audiometric findings of the disease have not been described. This is probably due to the rapid progression of the disease which often leads to total disability or even death (Moser 2000, 2001; Peters et al. 2004). Moser HW in 2000 reported that CCALD seems to be the most grievous type of this disease because of its rapid progress and poor prognosis which result in loss of physical function and in a short life expectancy.

8.5 Evaluation of Hearing in ALD

A standard hearing test for patients is pure tone audiometry. For infants, toddlers, and younger children, behavioral observation audiometry (BOA), conditioned orientation reflex audiometry (COR), and play audiometry are attempted and are used based on the patients' chronological or developmental age. Word discrimination tests (WDC), the environmental sound discrimination, token tests, dichotic listening tests (DLT), and sound lateralization tests are designated to evaluate

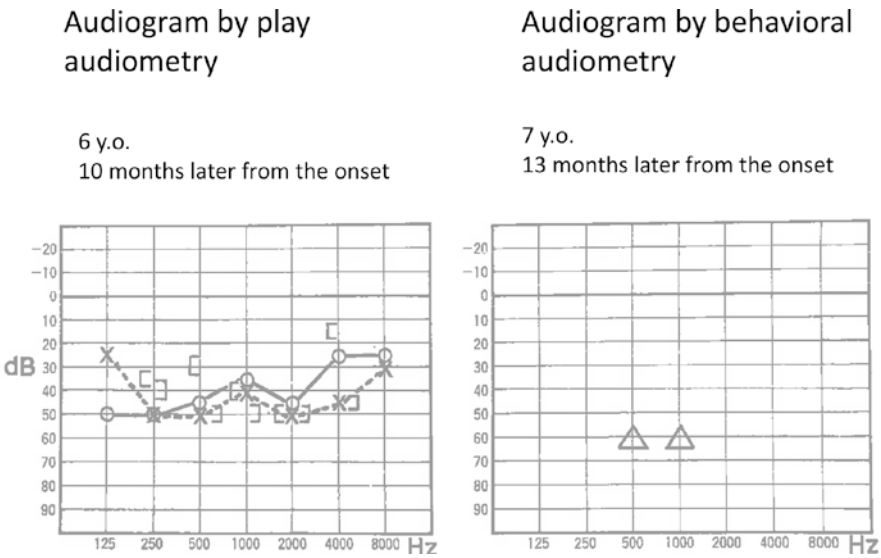

Fig. 8.2 Serial change of audiogram in a patient with ALD (Kaga et al. 1980)

precisely auditory cognitive function. Objective tests of auditory function include auditory brainstem responses (ABR) and otoacoustic emissions (OAEs). At the beginning of the disease, some patients request repetitions of speech input or they simply declare that they cannot hear (Fig. 8.2). Because of this, these patients are often misdiagnosed with a psychological reaction and a hearing impairment is not considered.

Hearing assessment in symptomatic patients with CCALD has indicated that a significant percentage of these patients had hearing impairment to some degree (Kaga et al. 2015).

To better understand auditory agnosia in ALD patients, the author presents three ALD patients with typical auditory agnosia which was severe and was difficult to understand initially, by family members and clinicians during the early clinical course of the disease.

8.6 Case Reports of Japanese Patients with ALD and Auditory Agnosia (Furushima et al. 2015)

8.6.1 Case Histories of Three Patients

8.6.1.1 Patient 1

This patient was a 3-year-old boy. He began to respond poorly when called and to ask back frequently to have incoming speech to be reacted. His hearing test at school was normal. In that his hearing continued to decline, he was seen by an

otolaryngologist 3 months later. His pure tone audiogram was normal at two visits to this clinic. It gradually became difficult for him to converse and he then lost the ability on the phone. He seemed not to comprehend his own hearing difficulty. This was later thought to be anosognosia. Other than his hearing problems he was completely normal. He was referred to a hospital at 13 years and 4 months of age. He was then diagnosed with CALD because of brain lesions on his MRI, elevated plasma VLCFA, and the presence of mutation of the *ABCD1* gene. His adrenal function was normal.

His condition prompted further neuropsychological and neurophysiological evaluation and he was thus referred to us. At our first encounter with him, he could only answer very simple questions such as his name or his age. His corrected visual acuity was 0.1 in his left eye and 0.6 in his right eye. He was found to have a left homonymous quadrantanopia. His pupils were dilated and reacted sluggishly to light. No pyramidal, cerebellar nor sensorineural signs were evident. Left to right transport impairment of tactile sensation and positional information was intact.

8.6.1.2 Patient 2

This patient was an 11-year-old boy. He began to complain of difficulty and fatigue with hearing other people's speech. He often did not respond to instructions given to him and he was thought to be absent-minded. His teacher noticed that he had poor reactions when he was called upon, he looked at his textbook upside down, he wore his gym suits backward (later it was thought to be a dressing apraxia) and he wrote confused and inaccurate letters. One year later he visited a psychiatric clinic whereupon he was referred to a university hospital. He then visited a pediatric clinic and was subsequently referred to a university hospital and he was diagnosed with CALD. The MRI showed characteristic signal changes, a high titer of VLCFA and a mutation of the *ABCD1* gene. His ABR was normal. Left homonymous hemianopia was detected and he had partial adrenal insufficiency. He gradually became short-tempered. Six months after the onset of his disease, he was referred to our clinic for detailed evaluation. At the time his physical examination was normal and he had no abnormal skin pigmentation. He could only engage in short and simple conversation. His deep tendon reflexes were exaggerated on his lower extremities although his muscle tonus was normal. Response to both tactile and painful stimuli was unstable. Position and vibratory senses were impaired over his left lower limb.

His SVR and MMN findings are presented in Fig. 8.3.

8.6.1.3 Patient 3

This patient was a 10-year-old boy. He did well until his 10th birthday and began to respond less and less when he was spoken to. He began to move slowly, become inactive (stagnated), and he ceased spending time with his friends. His school performance declined. Five months later his hearing was found to be normal by an

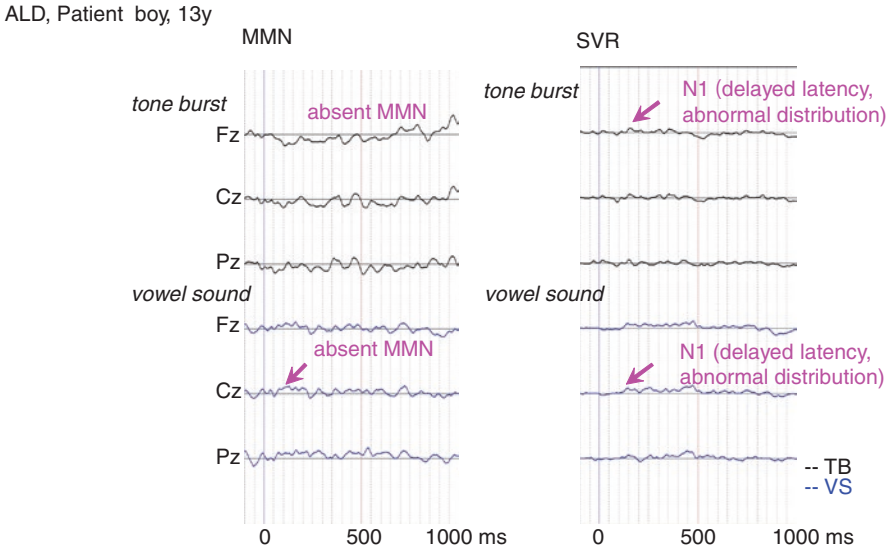

Fig. 8.3 MMN and SVR of a patient with ALD. 13 years old, boy

otolaryngologist; however, his response to voices on the phone decreased and he often asked speakers to repeat themselves. He was consequently referred to a pediatrician who made the diagnosis of CALD based on the following findings: brain lesions on his MRI, elevated VLCFA, and intellectual deterioration. Adrenal function was normal.

At 10 years and 9 months of age, he was referred to us for further evaluation. His physical examinations were normal. He displayed emotional incontinence and marked separation anxiety from his mother. On confrontation, he had a left-sided constriction of his visual field. His Achilles tendon reflexes were exaggerated and an ankle clonus was found in his right lower limb. Tactile, positional, and vibratory senses were normal.

8.6.2 MRIs of the Above Patients

8.6.2.1 Patient 1 (Fig. 8.4a)

In Fig. 8.4a, axial sections of FLAIR images from patient 1 and a coronal section of enhanced T1-weighed image are shown. FLAIR images indicated signal intensity changes in the auditory pathway (bilateral brachium of the inferior colliculus to medial geniculate body with right auditory radiation) and visual pathway changes over the bilateral lateral geniculate body with right optic radiation. Material-enhanced T1-weighted images revealed enhanced activity in his left medial geniculate body.

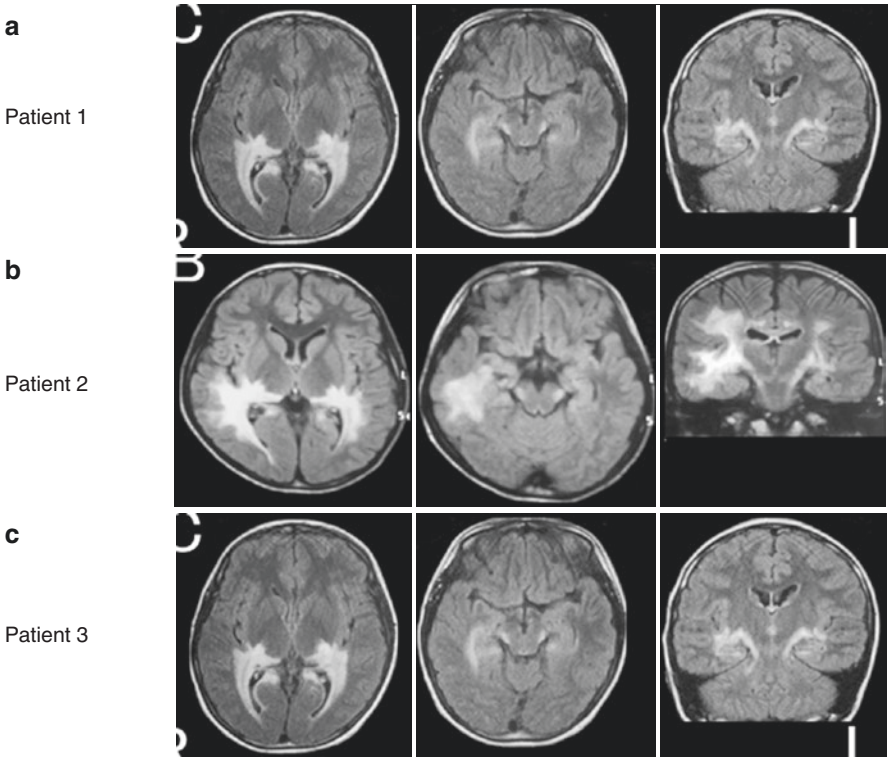

Fig. 8.4 MRI of three patients with auditory agnosia due to ALD (Furushima et al. 2015)

8.6.2.2 **Patient 2** (Fig. 8.4b)

Axial and coronal sections of his FLAIR images are also presented. FLAIR images show signal intensity changes in his auditory pathway (bilateral trapezius body ~ lateral lemunisci ~ brachium of the inferior colliculus to the medial geniculate body ~ auditory radiation) and signal intensity changes in his visual pathway (bilateral lateral geniculate body ~ optic radiation) and the splenium of corpus callosum.

8.6.2.3 **Patient 3** (Fig. 8.4c)

The axial and coronal sections of FLAIR images in patient 3 are presented. The flair images show signal intensity changes in the auditory pathways (bilateral brachium of the inferior colliculis to medial geniculate body to auditory radiation) and visual pathway intensity changes bilateral lateral geniculate bodies to optic radiation.

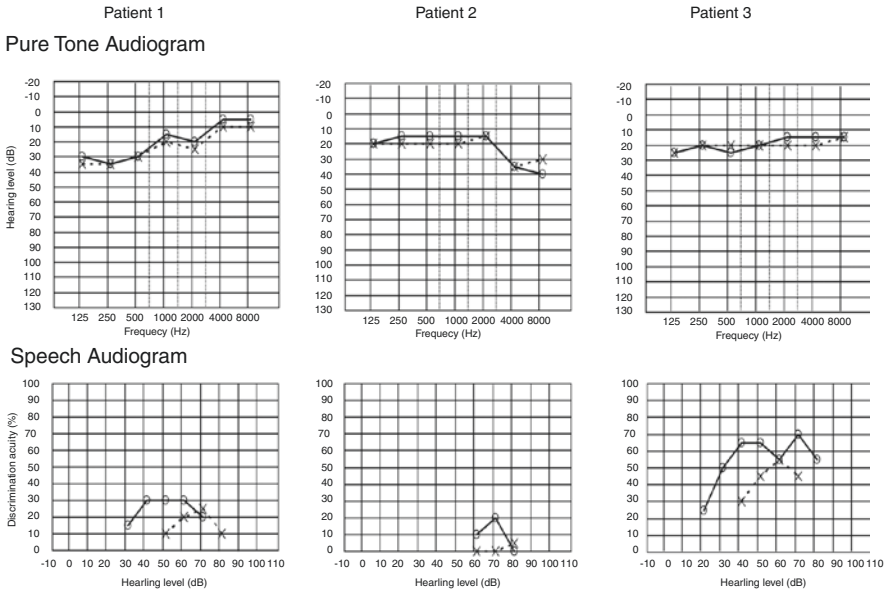

Fig. 8.5 Audiogram of three patients with auditory agnosia due to ALD (Furushima et al. 2015). All patients showed an almost normal pure tone audiogram but markedly abnormal speech audiogram

8.6.3 Audiograms

Pure tone audiograms and word discrimination test scores for each patient are presented in Fig. 8.5.

In each case, when compared to their pure tone audiogram findings, these patients' word discrimination scores were markedly worse. This finding delineates auditory verbal agnosia and nonverbal agnosia.

Serial change of audiogram was presented by Kaga in 1980.

8.6.4 ABR Findings

ABR tracings are presented in Fig. 8.6.

The basic waveform configurations and response thresholds were almost normal in each patient. The precise evaluation of each patient's evoked waveforms is described below:

Pt 1 Interpeak latency of Wave I and III was prolonged on the left side. The threshold of wave V was normal.

Pt 2 Interpeak latency of Wave I and V was prolonged on the left. The threshold of wave V was normal.

Pt 3 Interpeak latency of Wave I and V was prolonged bilaterally. The threshold of wave V was normal. Serial change of ABRs is presented by Kaga et al. in 1980 (Fig. 8.7) and Inagaki et al. in 2006 (Fig. 8.8).

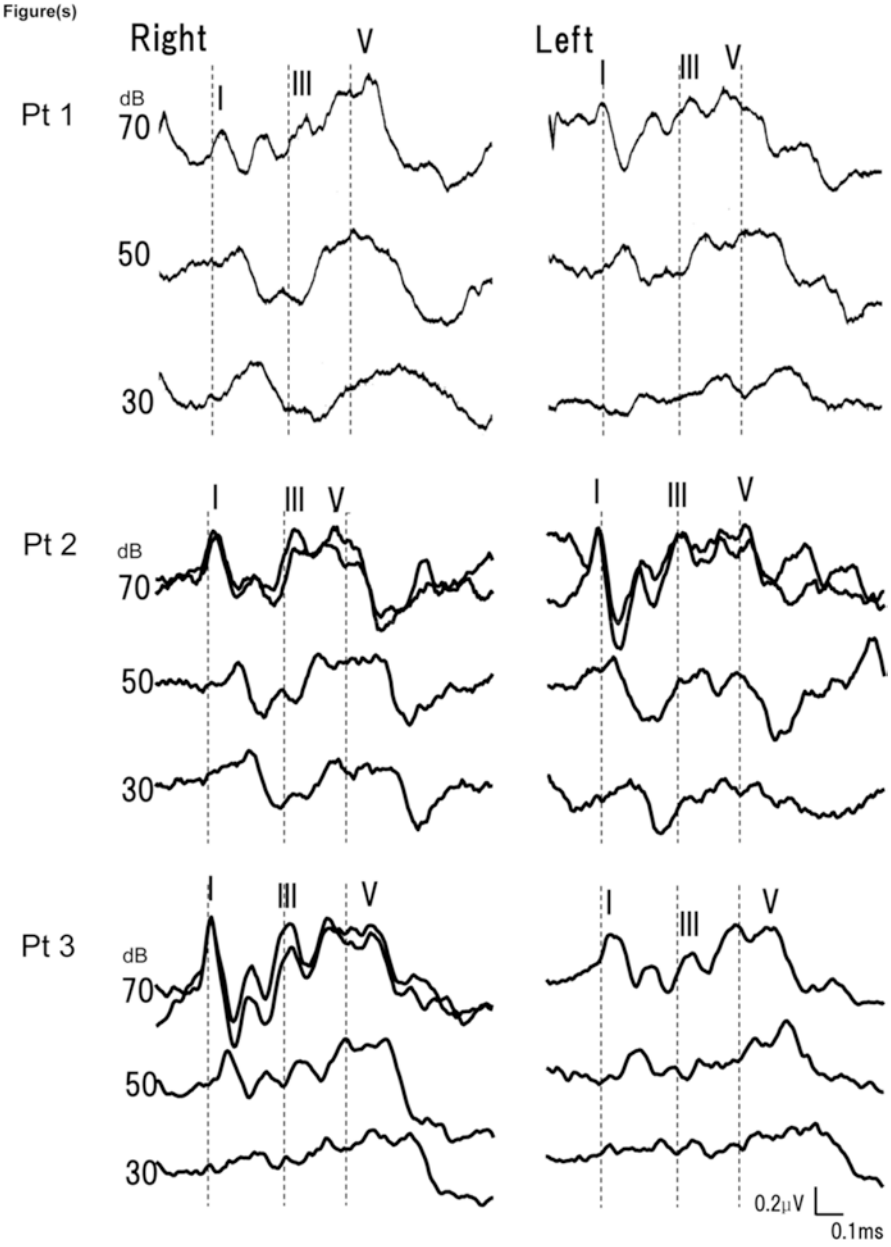

Fig. 8.6 ABR of three patients with auditory agnosia due to ALD (Furushima et al. 2015). All patients showed normal waveform of ABR and wave V threshold. Patient 3 showed prolonged latency of wave V and central conduction

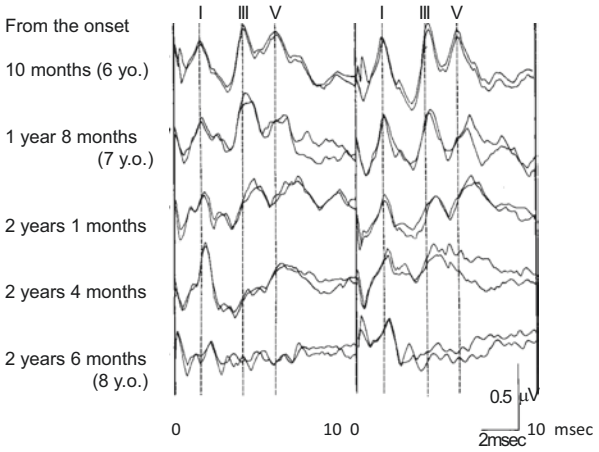

Fig. 8.7 Serial change of ABR in a patient with ALD (Kaga et al. 1980, altered by the author)

8.6.5 SVR and MMN

The evoked N1s of the slow vertex response (SVR) and the evoked mismatch negativity (MMN) response to verbal and nonverbal stimuli are useful to evaluate the objective and unconscious cognition of verbal and nonverbal auditory stimuli. In this section, we will show the results of SVR and MMN to nonverbal (tone burst, [1KHz][2KHz]) and verbal (vowel sound, [a][æ]) stimuli. The occurence of the stimuli is 80% for the former and 20% for the latter, in each stimuli. These results point out the disparity of findings between the use of these different stimuli in patients with auditory agnosia due to ALD. This stimulus-dependent disparity between results of SVR and MMN in patient 2 is shown in Fig. 8.9.

Serial change of SVR was presented by Kaga (Fig. 8.10).

8.7 Summary

8.7.1 Hearing Impairment

The frequency of hearing impairment as the initial symptom of ALD has been reported to be between 6 and 7% (childhood cerebral type 3/46 and adolescent cerebral type 1/14, Suzuki et al. 2005), 8% in childhood cerebral type $N = 160$ (The Metabolics & Molecular Bases of Inherited diseases, 8th edition) and 13% (childhood and adolescent cerebral type 5/38, Tanaka et al. 1989).

All three of the above-described patients had in common: (1) a severe loss of word discrimination scores compared to their relatively normal pure tone acuity, (2) good ability to recognize, understand, and respond a non-auditory route or

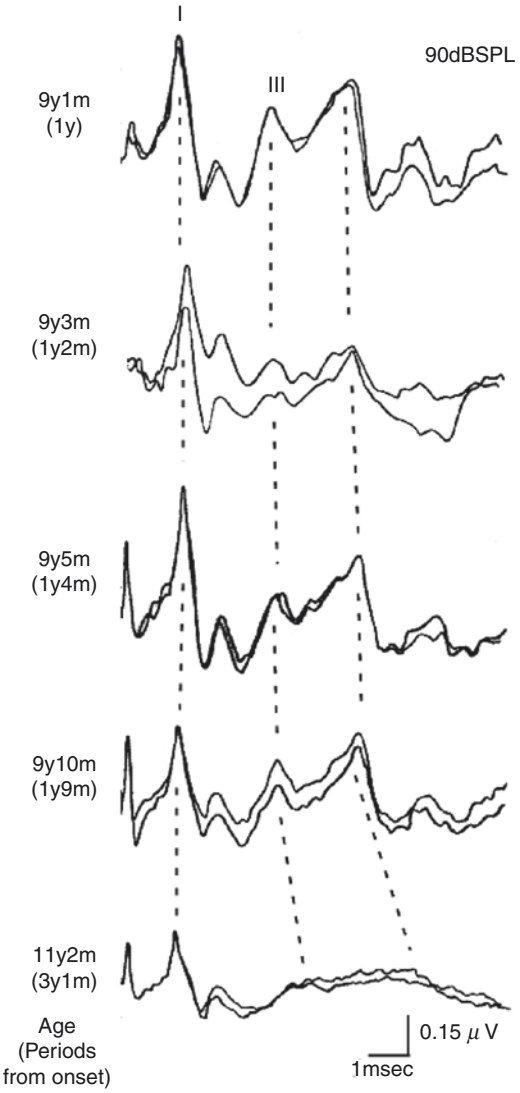

Fig. 8.8 Serial change of ABR in a patient with ALD (Inagaki et al. 2006). The patient's motor and mental development was normal until 8 years and 1 month old. His first symptom was a defect of the visual field. He was admitted to a hospital aged 8 years and 11 months. He gradually lost his ability and became bedridden at last. His ABR was normal in shape, latency, and amplitude after the onset of his disease (9 years and 1 month). However, interpeak latency of I–V gradually became prolonged and all waves reduced their amplitude. Three years from the onset, wave V disappeared finally. Figures noted in blankets are the time course from his onset of the disease

appropriately to help that which was spoken to them by using non-auditory route, they could perform quite well, (3) no paraphasia was noted in any patient. We thus determined that these patients had auditory agnosia and not aphasia. These patients could recognize verbal and environmental sounds when they were accompanied by visual aids (presented with pictures and lip reading). Verbal stimuli coming from outside their visual field was hard to recognize for these patients. Conversations on the telephone were very difficult for them because they had no visual cues.

8.7.2 *Auditory and Other Symptoms Caused by Localized Brain Lesions in Patients with ALD*

Abnormal MRIs confirmed bilateral medial geniculate body abnormalities and unilateral or bilateral auditory radiation in all three of the above ALD patients. ALD is basically a disease of the white matter, lesions in the auditory cortex of these patients were not observed at least not in the early stage of their disease. Thus, auditory agnosia occurs due to a disconnection between the auditory cortex and the subcortical white matter. Auditory agnosia was therefore a clinical diagnosis based on finding (by MRI) localized white matter lesions each of these in these patients' auditory pathways.

Moreover, there are some patients who showed agnosia of their disease, and apraxia while dressing. Those symptoms were considered as due to cortical lesions. However, ALD can play a role in emerging temporal, parietal, and frontal signs and symptoms based on the extensiveness of the white matter lesions when they can be tested by neurologically.

Serial change could be evaluated clinically and nerophysiologically.

There are other types of leukodystrophy such as Groboid cell leukodystrophy (Krabbe disease), metachromatic leukodystrophy, Alexander disease, and others. These disorders also present a slow progressive course with the possibility of developing emerging focal cortical lesions as seen in ALD. However, patients with these

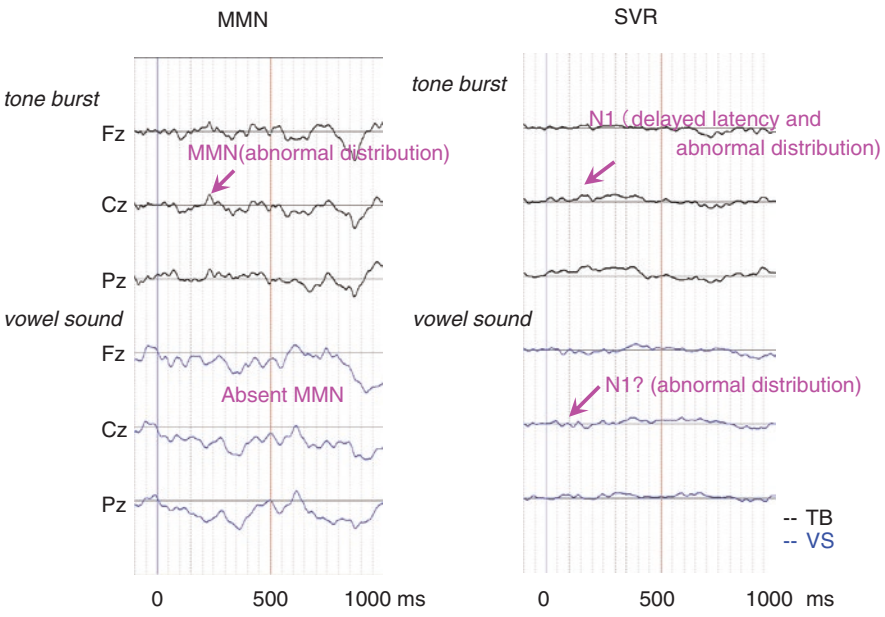

Fig. 8.9 Patient 2, ALD, boy, 11 years (Furushima et al. 2015)

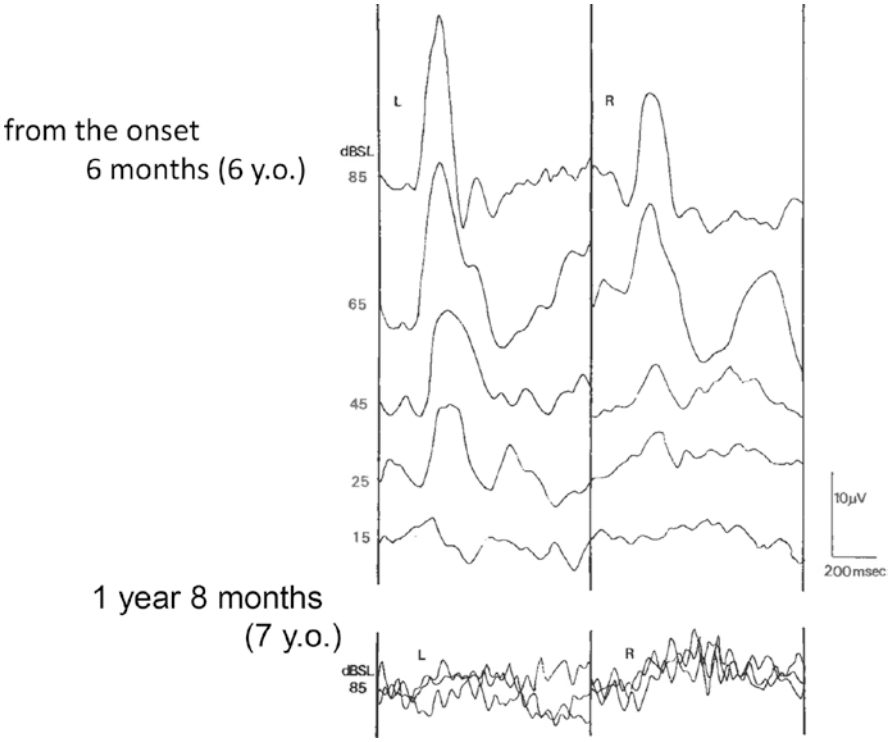

Fig. 8.10 Serial change of SVR in a patient with ALD (Kaga et al. 1980)

diseases rarely show symptoms caused by localized brain lesions. This is because these diseases usually progress rapidly in the brain and the lesion expansion is almost uniform. Therefore, it is very difficult to recognize symptoms based only on MRI images of localized brain lesions. Even during the clinical evaluation of an ALD patient, such symptoms may often be overlooked.

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Chapter 9
Cerebrovascular Accidents

Abstract Cerebrovascular accidents in infants and children are caused by cerebrovascular hemorrhage due to head trauma or leukemia or stenosis of the anomalous cerebral artery (Moyamoya's disease). Auditory agnosia is a manifestation of lost auditory perception following bilateral auditory cortex lesions which occur immediately subsequent to cerebrovascular accidents.

We herein present two patients with auditory agnosia. Auditory agnosia in Patient 1 was precipitated by an immediate onset of cerebral hemorrhaging due to leukemia in the bilateral superior temporal lobes. On the other hand, the auditory agnosia was caused by Moyamoya's disease with the subsequent stenosis of the bilateral middle cerebral arteries. Both patients show that it is important to provide speech and language therapy matched to the needs of each patient and to maintain follow-up over the long term, often for years.

Keywords Auditory agnosia · Cerebrovascular accidents · Leukemia · Moyamoya's disease

9.1 Introduction

Auditory agnosia following cerebrovascular accidents in infants and children is caused by head trauma, hematological diseases, or anomalous stenosis of the cerebral arteries (Moyamoya's disease). Two cases with auditory agnosia are presented.

M. Kaga, K. Kaga, *Landau-Kleffner Syndrome and Central Auditory Disorders in Children*, Modern Otology and Neurotology,
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9.2 Patient 1

A 13-year-old boy.

Diagnosis: Bilateral temporal lobe hemorrhage caused by lymphatic leukemia.

A male junior high school student (age 13) suffered a cerebral hemorrhage in his bilateral temporal lobes due to acute lymphatic leukemia. Afterward, he manifested sensory aphasia and loss of hearing. His brain MRI illustrated bilateral auditory cortex brain infarctions and in Wernicke's speech center (Fig. 9.1a). Pure tone audiometry showed profound sensory neural hearing loss (Fig. 9.1b). On the other hand, his ABR revealed normal thresholds in both ears (Fig. 9.1c). Prior to his bilateral temporal lobe cerebrovascular accidents, his speech and hearing were normal. However, after this sudden onset cerebrovascular accident, he could not react to any sounds. The audiological examination revealed his loss of auditory perception and comprehension. He could not perceive speech sounds, music, nor environmental sounds. Because he manifested a mild left hemiparesis, he enrolled, mainstream, in

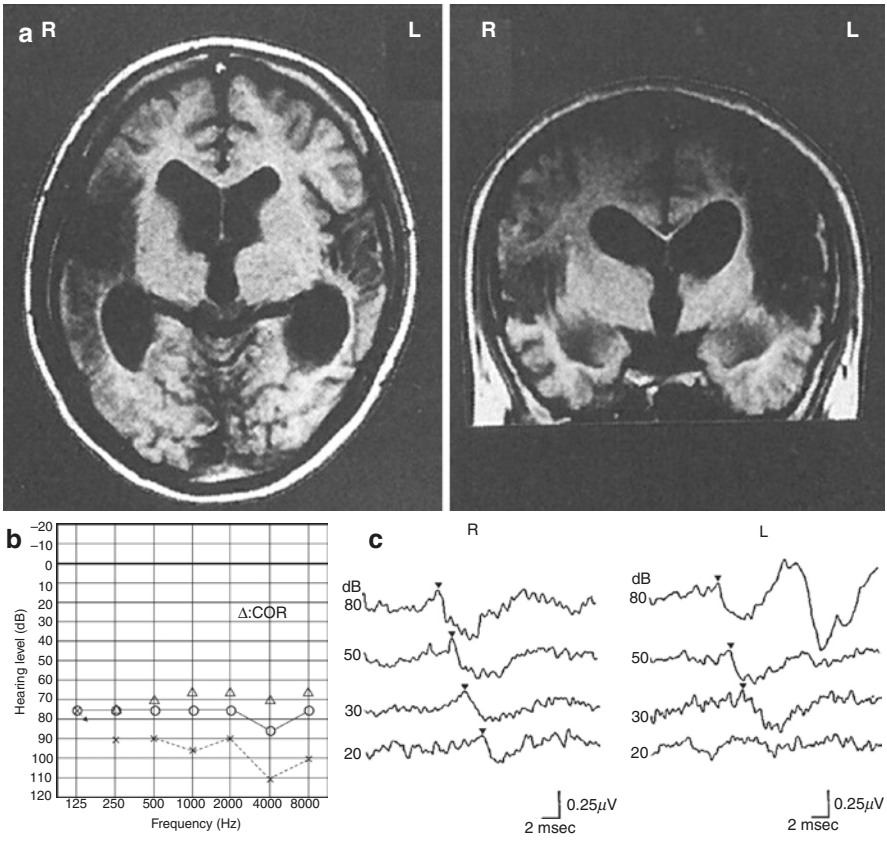

Fig. 9.1 Case 1 (**a**) Brain MRI showing lesions in the bilateral auditory cortices and Wernicke language center. (**b**) COR reveals moderate sensory neural hearing loss in both ears. (**c**) Thresholds of ABRs in both ears demonstrate normal thresholds at 20 dBHL (Shindo 1993)

a special school for the hearing impaired during his junior high school year. He quickly learned sign language and it became possible for him to communicate with others again by using this visual language communication method (Shindo 1993).

9.3 Patient 2

A 24-year-old female.

Diagnosis: Stenosis of the middle cerebral arteries subsequent to Moyamoya's disease.

When she was 10 years old, while she was in elementary school, she was diagnosed with Moyamoya's disease which caused a stenosis of her cerebral artery. At 15 years of age, while in junior high school, she incurred a left temporal hemiparesis but she recovered completely with no hearing problems. She was diagnosed with stenosis of the middle cerebral artery due to Moyamoya's disease in the right hemisphere. Although she recovered completely from the right hemiparesis she still complained of loss of hearing bilaterally. The angiography of her brain disclosed obstruction of the middle cerebral arteries in both hemispheres. She was diagnosed with auditory agnosia caused by Moyamoya's disease. Fortunately, she did not manifest any hemiparesis or aphasia.

The lesions in her brain were found to be located bilaterally in the auditory cortex with radiation by MRI (Fig. 9.2a). Pure tone audiometry showed a normal hearing threshold 2 years after onset (Fig. 9.2b), and ABRs (Fig. 9.2c) and the K complex on her electroencephalogram (EEG) were well elicited (Fig. 9.2d). Auditory monosyllabic tests of both ears scored only 2% and her Token test score of 22% indicated severely impaired auditory perception and recognition. Auditory training for perception and recognition was provided. However, in the lip-reading tests, the score for lip-reading plus listening for words increased to 48%, which was markedly better than that for lip-reading alone (12%) or listening alone (10%). For the short sentence recognition test, her score for lip-reading plus listening (20%) was little better than that for lip-reading alone (0%) or listening alone (10%). In spite of her auditory agnosia, she could work temporally in a law office after high school. However, on follow-up, her pure tone audiometric findings showed a progressive sensory neural hearing (Fig. 9.2b).

9.4 Discussion

Disorders of auditory perception in children may result from *cerebrovascular accidents* which affect the bilateral internal carotid arteries (Kaga 2009) and appear, clinically, as auditory agnosia, i.e., the impossibility to recognize speech, environmental sounds, and music which the patient, however, admits to hearing, or *cortical deafness* giving rise to the feeling of being deaf which is out of scale with the pure tone audiogram and in spite of normal ABR threshold findings (Kaga et al. 2015).

The etiology of the two cases presented in this chapter was quite different. Case 1 was caused by a bilateral temporal lobe hemorrhage due to lymphatic leukemia.

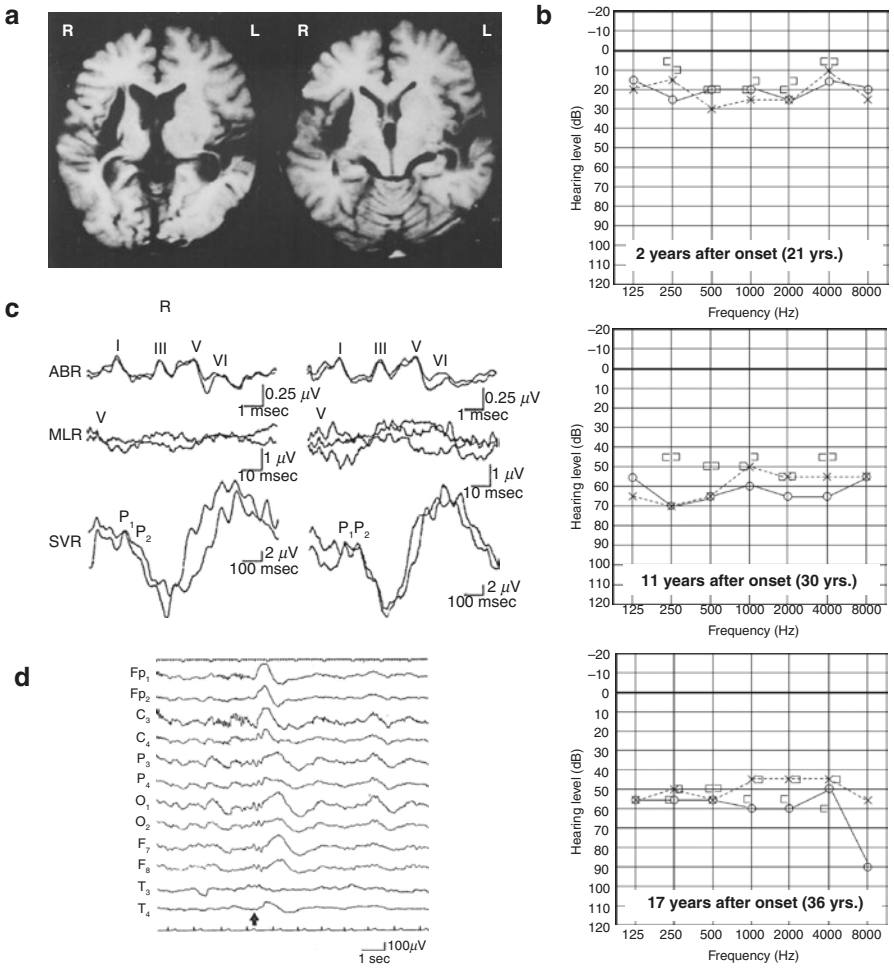

Fig. 9.2 Case 2. (**a**) MRI of the brain. The auditory radiation in the right hemisphere is lesioned and the auditory cortex and radiation in the left hemisphere are also damaged. (**b**) Pure tone audiometry showed progressive sensory neural hearing loss over time. (**c**) ABRs were normal as were slow vertex responses (SVRs) but middle latency responses (MLRs) were absent in both ears. (**d**) Electroencephalography (EEG) revealed that K complexes to a sound stimulus were recorded from all electrodes (**d**, arrow). Reused with permission from Kaga (2009)

Case 2 was caused by a stenosis of her right and left middle cerebral arteries due to Moyamoya's disease.

In Case 2, repeated pure tone audiometry revealed that bilaterally her thresholds elevated (poorer hearing levels) over time in spite of her normal ABR thresholds. Kaga et al. have reported neuropathology of an adult patient with auditory agnosia following bilateral temporal lobe lesions and progressive hearing loss over time (Kaga et al. 2000).

Postmortem neuropathological analysis of each patient's hemispheres revealed a total defect and neuronal loss of the superior temporal gyrus, including Heschl's gyrus, and total gliosis of the medial geniculate body. In the right hemisphere, examination revealed subcortical necrosis, gliosis in the center of the superior temporal gyrus, and partial gliosis of the medial geniculate body. The pathology examination supported the clinical results in which the patient's imperception of speech sound, music, and environmental sounds could be caused by progressive degeneration of the bilateral medial geniculate body.

In conclusion, degeneration of the medial geniculate body may have occurred as a result of retrograde degeneration due to bilateral auditory cortex lesions.

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Chapter 10
Auditory Agnosia in Children Due to Herpes Encephalitis

Abstract Five pediatric patients whose bilateral auditory cortices were damaged by herpes encephalitis at an early age were studied. Their brain CT and MRI scans demonstrated common bilateral lesions of the auditory cortices. Their auditory perception was evaluated by means of behavioral and objective hearing tests and auditory perception tests. Four patients showed mild or moderate hearing loss in the behavioral hearing test and on their ABRs but they did not manifest total deafness. Moreover, perception tests involving speech, environmental sounds, and music demonstrated that auditory perception ability had been mostly lost in all patients. On reaching school age, the patients were enrolled in schools for the deaf or special schools for handicapped children. A patient who was followed up for over 30 years ultimately showed profound hearing loss.

Keywords Auditory agnosia · Auditory cortex · Herpes encephalitis · ABR · Progressive deafness

10.1 Introduction

In adult patients, auditory agnosia is usually caused by two episodes of cerebral infarction, often due to cerebrovascular accidents or trauma. However, in pediatric cases, it is frequently caused by herpes encephalitis (Sugimoto et al. 1985; Kapur et al. 1994; Kaga et al. 2000, 2003). Auditory functions of pediatric patients have rarely been recorded and not well documented from developmental and educational standpoints (Kaga et al. 2003). Herein, we report five cases of children with auditory agnosia following herpes encephalitis who were studied from the neurotological, neuropsychological, and educational standpoints, in order to determine how they differ from adult cases.

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10.2 Case Reports

10.2.1 Patient 1

A right-handed girl whose delivery was uneventful. Her early development was normal and she responded well to auditory stimuli. When she was 6 months old she suffered from herpes encephalitis. A brain MRI revealed bilateral lesions of the auditory cortices and a left frontal lesion (Fig. 10.1). Subsequently, she became indifferent to sounds and could not distinguish any sounds. Conditioned orientation reflex (COR) audiometry showed threshold elevations of 60 dB HL (Fig. 10.2) but the ABR threshold was 20 dB HL (Fig. 10.3). She was diagnosed as having auditory agnosia as a sequela of herpes encephalitis. As she could still not speak at age of 6, she was enrolled in a school for handicapped children during her elementary, junior high, and senior high school years.

10.2.2 Patient 2

A right-handed boy whose delivery was uneventful. His early development was completely normal. He began to speak several words using mimicry when he was 12 months old. When he was 14 months old he suffered from herpes encephalitis

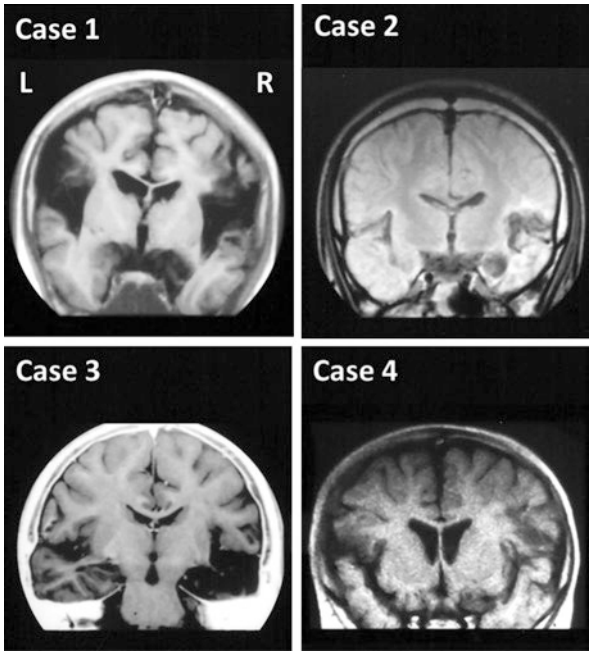

Fig. 10.1 Brain MRI of the four cases with herpes encephalitis. Note the bilateral lesions in the superior temporal gyri, including the auditory cortex. Reused from Kaga (2009) with permission

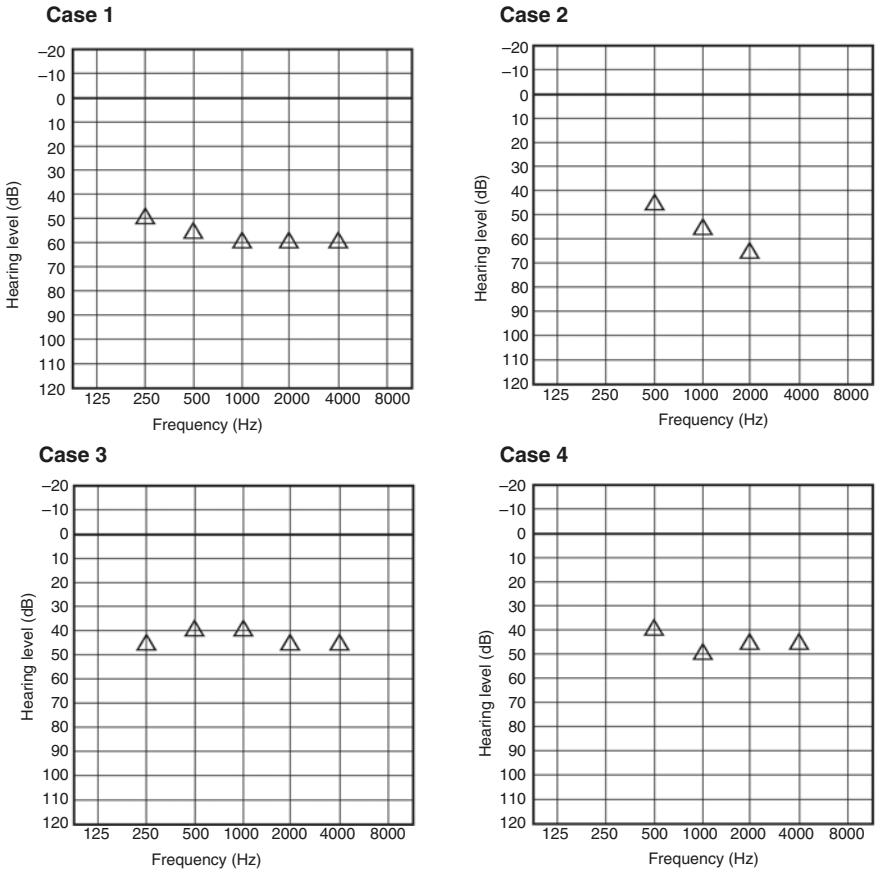

Fig. 10.2 Audiograms of the four cases with herpes encephalitis examined by means of COR audiometry because pure tone audiometry was difficult. Note the threshold elevation compared to age-matched controls. Reused from Kaga (2009) with permission

which was diagnosed based on his increased serum levels of herpes simplex virus antibody. At the age of 2 years, he still had spoken no intelligible words. Although he responded well to visual stimuli, he had no interest in auditory stimuli and only rarely responded to environmental sounds. COR audiometry revealed an increased threshold to 60 dB HL (Fig. 10.2). However, his ABR showed a normal threshold of 15 dB HL (Fig. 10.3). A brain MRI revealed lesions of his auditory cortices bitemporally that were more prominent in the right as opposed to the left hemisphere (Fig. 10.1). The patient was diagnosed with auditory agnosia as manifested by the destruction of the bilateral auditory cortex caused by herpes encephalitis. He was enrolled in a school for the deaf until graduation from high school. In his daily life, he can hear but he cannot distinguish speech, environmental sounds, and music. However, he can write and can communicate using sign language.

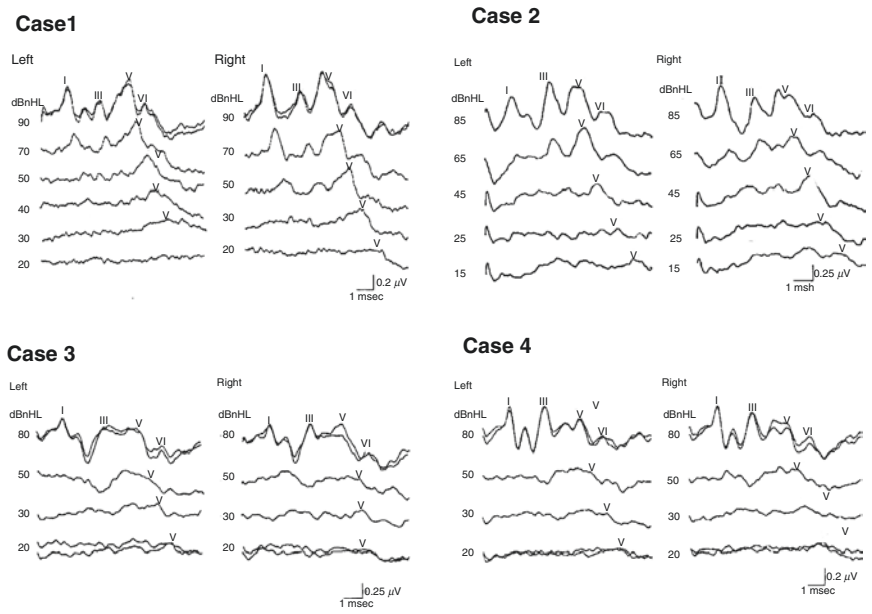

Fig. 10.3 ABRs of the four cases with herpes encephalitis showing normal configurations with wave I-VI and thresholds. Reused from Kaga (2009) with permission

10.2.3 Patient 3

A right-handed boy whose development was normal until the age of 1 year and 3 months when he suffered from herpes encephalitis. Upon examination, it was found that he did not respond to sound and could not speak any words. His brain MRI demonstrated bilateral lesions of the superior temporal gyrus, including the auditory cortex (Fig. 10.1). COR audiometry showed a threshold elevation of 50 dB HL (Fig. 10.2) but his ABR showed a normal threshold of 20 dB HL (Fig. 10.3). Speech discrimination, perception of environmental sounds, and music and auditory comprehension were all completely impaired. Speech therapy was started at 3 years and 6 months of age. Sign language training (cued speech) was introduced at a school for the deaf. At the age of 6 years, he could use >220 words and two-word sentences for communication. He is now 17 years old and a student at a high school for the deaf. He continues to use sign language to communicate.

10.2.4 Patient 4

A right-handed boy whose delivery was uneventful. His development was normal. He could hear and talk with friends of the same age until the age of 2 years and 7 months when he suffered from herpes encephalitis. Thereafter, he did not respond

to any sound stimuli or speak any words. His brain MRI demonstrated bilateral lesions of the superior temporal gyri including the auditory cortex (Fig. 10.1). COR audiometry showed a threshold elevation of 50 dB HL (Fig. 10.2) but ABRs revealed normal thresholds bilaterally of 20 dB HL (Fig. 10.3). Subsequently, the patient responded to several environmental sounds and voices but he could not distinguish any speech or music. He was enrolled in a school for the deaf. Initially, he communicated using gestures. At the age of 5 years sign language was introduced and he could use two- and three-word sentences for communication. However, fingerspelling, letters, and lip-reading remained difficult for him to learn.

10.2.5 Patient 5

A right-handed boy whose development was normal until the age of 1 year when he suffered from herpes encephalitis. His brain MRI demonstrated bilateral lesions of the auditory cortices (Fig. 10.4). Afterward, he lost speech and hearing. With the exception of speech and hearing problems, he did not manifest any neurological problems. When he was 1 year and 6 months, he was diagnosed with auditory agnosia. Afterward, he was provided speech and language rehabilitation. During his kindergarten period and early into his elementary school age, cued speech training was given to him. However, after late in his elementary school age, finger letters and sign language education were provided until the end of his high school. In Fig. 10.5, his pure tone audiograms at his age of 5 and 28 years are shown revealing normal hearing thresholds. Figure 10.6 revealed normal DPOAEs at age 28. In Fig. 10.7, his ABRs at his age of 5 and 28 years revealed normal hearing. These audiological examinations revealed no problems in his middle and inner ears and brainstem auditory pathway. However, he completely lost his hearing bilaterally at 28 years of age.

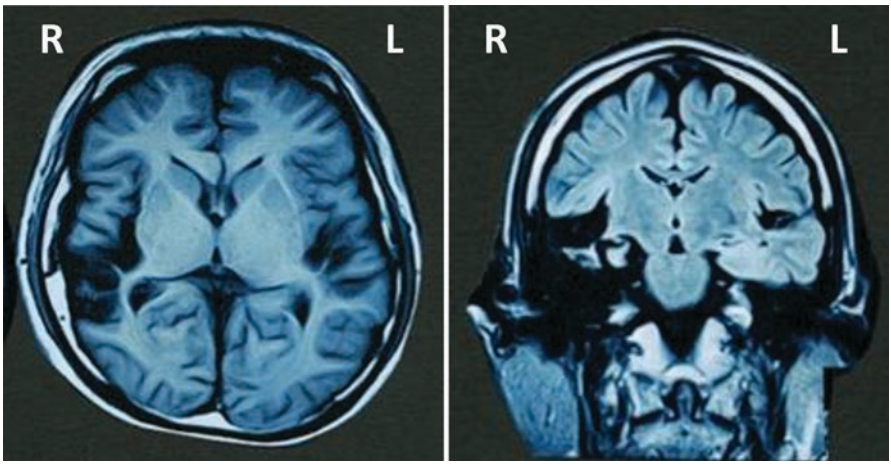

Fig. 10.4 Brain MRI of Case 5 at the age of 28 years old

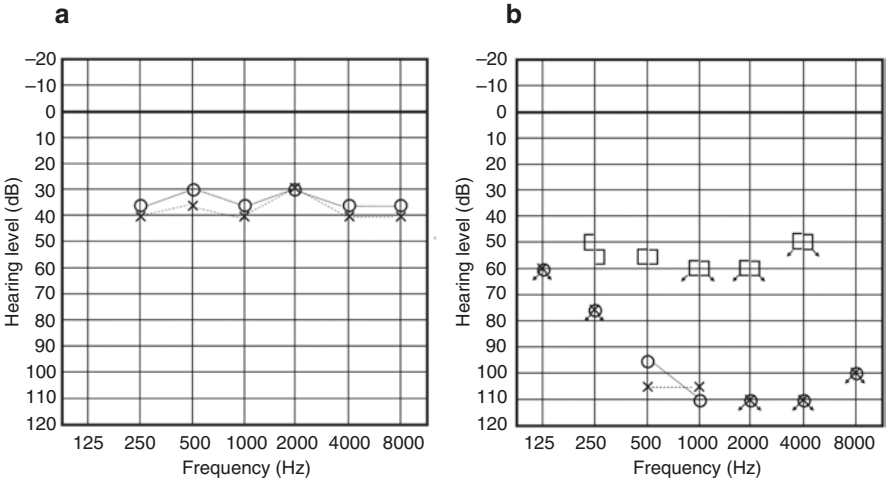

Fig. 10.5 Pure tone audiogram at the age of 5 (**a**) and at 28 (**b**) years old

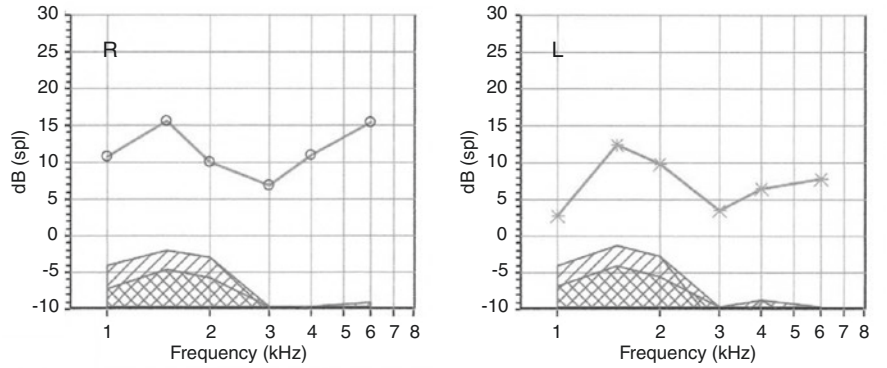

Fig. 10.6 DPOAEs at the age of 28 years old

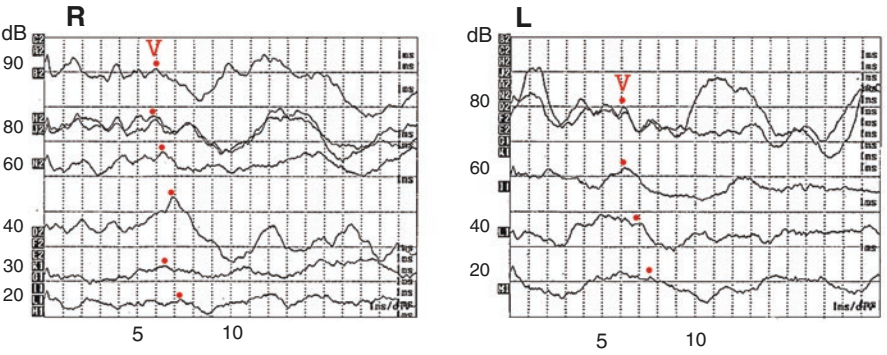

Fig. 10.7 ABRs at the age of 28 years old

10.3 Discussion

Herpes simplex encephalitis is known to lead to focal brain necrosis particularly in the temporal orbitofrontal regions of the brain. However, language-related sequelae in children caused by focal brain lesions are very limited. Our five patients, having being diagnosed with herpes encephalitis, showed common bilateral temporal lesions of the auditory cortices which underlie typical auditory agnosia. The early onset of auditory agnosia in these patients made their education very difficult. Four of the patients went to schools for the deaf and one was educated at a school for handicapped children. Their audiograms showed residual hearing except, in Case 5, he, at the age of 28 years old, gradually lost his hearing becoming practically deaf. However, all of the patients can now read and write Japanese characters although not perfectly. Because of their very slow development of the concepts of grammar, they experienced difficulty in communicating effectively with others. Written communication became almost impossible despite retaining some writing ability. However, sign language became very useful as a communication tool for all of them.

Communication training and education of these patients led to some, but not complete, improvement in their communication abilities. In the present educational setting, schools for the deaf are better than other schools because they cater to such very rare cases as these who require special education.

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Chapter 11
Transient Auditory Agnosia/Cortical Deafness During the Recovery Phase of Acute Encephalopathy of Unknown Origin

Abstract The case of a 3-year-old girl who showed transient auditory agnosia (or cortical deafness) during the recovery phase of atypical biphasic encephalopathy is described. Bitemporal lesions that resolved within a short period (several weeks at best) were suggested by MRI. Because of the patient's age, a precise neuropsychological examination could not be performed. However, her symptoms could not be explained by her temporally depressed cognitive ability. The reason was the patient's well-preserved visual cognition compared with absent auditory cognition despite normal ABR. The case details are described herein for further interpretation in future studies.

Keywords Transient auditory agnosia · Cortical deafness · Complication of encephalopathy

11.1 Introduction

Influenza, roseola (exanthema subitum), and other febrile diseases often result in mild to severe encephalitis/encephalopathy with loss of consciousness, convulsions, and residual brain dysfunction both in infants and children.

Any encephalitis or encephalopathy often brings severe to profound mental retardation and sometimes hearing impairment of cochlear origin as their sequela.

Awaya reported biphasic encephalopathy (Awaya 1989). Fever, convulsions, and consciousness disturbance occur at first. Then consciousness recovers for a few days but again intractable partial seizures and severe neurological complications follow thereafter. He found that some of these patients had central hearing impairment by the biphasic encephalopathy or encephalitis (Awaya and Fukuyama 1986; Fukuyma et al. 1988 "Reports to the Ministry of Health and Welfare, Japan in 1988").

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A diagnosis of the central hearing impairment during the course of this type of biphasic encephalopathy reveals poor responses to any loud sounds or loud speech but with normal ABRs to the high-intensity sound stimuli. More patients could be found if the ABR would be recorded for all such patients during their illness.

This type of encephalopathy has been focused on attention especially in intractable epilepsy and the epileptogenesis of the disease especially among Japanese child neurologists. This is named as acute encephalitis with refractory, repetitive partial seizures (AERRPS) (Sakuma et al. 2010). AERRPS has been energetically investigated and became a definitive disease entity. In the process, auditory agnosia as a symptom or a sequel disappeared as the symptom of the disease. Maybe it is due to the intractable epilepsy and deterioration of intellectual and motor activities that are considered as most serious in each patient.

The below patient had biphasic encephalopathy followed by a febrile disease with convulsive status. During her recovery phase of her disease, she had transient central auditory impairment. Discrepancy of cognition through hearing and vision was evident. Thus we thought she had temporal auditory agnosia/cortical deafness with relatively intact visual cognition in the course of her biphasic encephalopathy. She remained undiagnosed but I try to emphasize the presence of central auditory dysfunction in the clinical situation.

11.2 Patient: 3 Years Old, Female

Her chief complaint was loss of words after fever and convulsive status.

Her developmental milestones were normal. When she was 3 years old, she became febrile with a temperature up to 38.0 °C. In the evening, she had generalized clonic convulsions followed by twitching of her left leg. Her seizure ceased after 50 min following diazepam infusion at an emergency hospital. She was diagnosed as acute encephalopathy and received most accurate treatment with antimicrobial/antiviral agents and necessary supportive care. A CT scan has revealed the presence of diffuse brain edema (no image). On the second day of the disease, she was afebrile but was drowsy. On the third day of her hospitalization, she opened her eyes, became conscious, and said her name and that she would like to go home. On day 5, she became restless and lost her speech. T2-weighed MRI was evaluated as the presence of mild brain atrophy and relatively high signals from both temporal lobes (no image). Two weeks after the onset of her disease, she was referred to us for the further evaluation of the sequelae of her biphasic encephalopathy. On admission, she was awake but had no interest to her surroundings, including her parents. She had mild weakness in her left lower extremities. She swayed her body back and forth purposelessly as often seen in autistic children. She did not respond to any speech nor to loud environmental sounds. Her thresholds and the latencies of her ABR tracings were within normal limits (Fig. 11.1). Her attitude toward her parents and visual stimuli gradually improved day by day. On day 28, she continued not to respond to any speech or very loud sounds. However, she fully recognized her

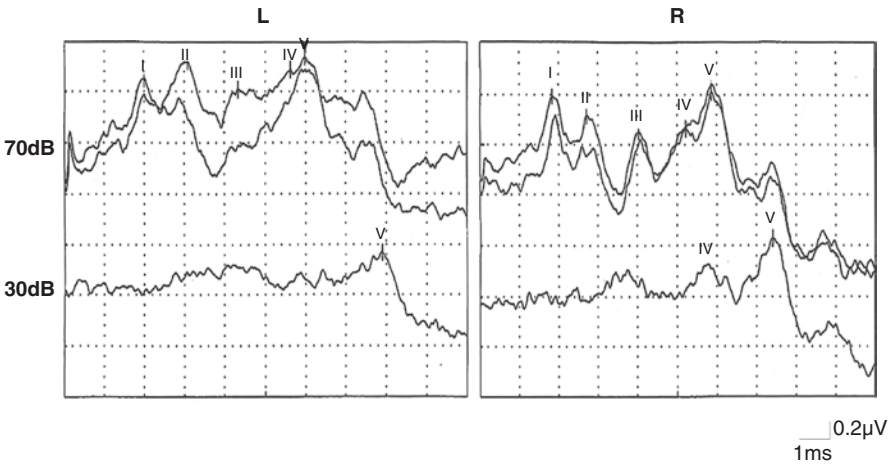

Fig. 11.1 ABR of the patient

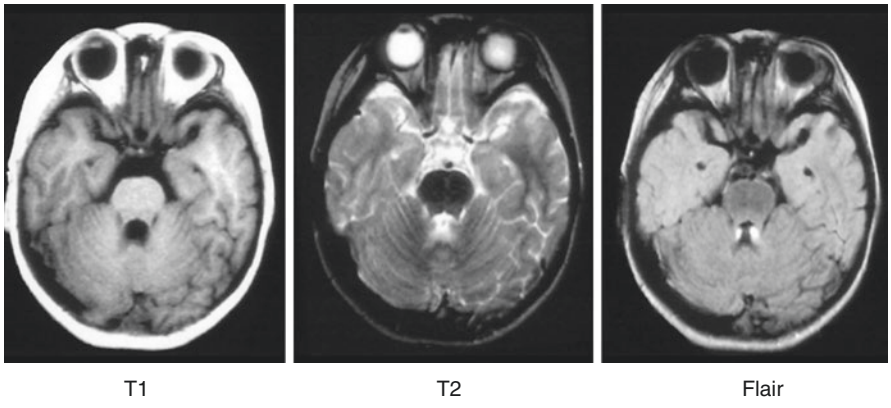

Fig. 11.2 MRI of the patient, recovery phase

mother and enjoyed her favorite toys. At day 38, her responses to speech, environmental sounds, and visible stimuli returned to almost normal. When she was discharged, on day 45, she could recognize her favorite animation character, said the names of her friends and obeyed simple commands and answered simple questions. CT and MRI scans had been returned to normal (Fig. 11.2). No etiological virus was determined in this patient.

In summary, she had temporarily lost response to auditory stimuli which was thought to be the central origin. Temporal discrepancy of cognition through visual and auditory route was remarkable but improved within a relatively short period.

Comment: Her auditory agnosia or cortical deafness was transient. Her unresponsiveness to auditory stimuli might be due to her temporal intellectual

deterioration. However, a definite discrepancy between her very good response to visual and almost no response to auditory stimuli cannot be explained by the intellectual situation during her recovery phase of her disease. No precise neuropsychological examinations could be performed despite the history of bitemporal lesions suggested by MRI.

The author ventured to describe the clinical features of this patient despite the diagnostic shortage which should be determined by the medical examinations. I just to show her clinical features and to expect future exact resolution or interpretation of this phenomenon.

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Chapter 12
Pelizaeus–Merzbacher Disease

Abstract Pelizaeus-Merzbacher disease (PMD) is classified into six types. Patients with type II PMD show congenital nystagmus, hypotonia, rigidity of the trunk and extremities, and mental and speech retardation as the main clinical symptoms. Brain MRIs show a high signal intensity in the white matter and a low signal intensity in the gray matter of the cerebrum. ABR tracings commonly show only waves I and II.

We herein report four children with Pelizaeus–Merzbacher disease whose brain MRIs demonstrated abnormalities in the cerebrum and their ABR tracings showed only waves I and II.

Keywords ABR · MRI · Auditory cortex · Dysmyelination · Horizontal nystagmus

12.1 Introduction

Pelizaeus reported the first case of Pelizaeus–Merzbacher disease (PMD) in 1885 (Pelizaeus, Arch Psychiat Nervenkr 1885). PMD, an X-linked recessive inheritance disease, manifests as dysmyelination in the central nervous system (CNS) and is usually regarded as a kind of leukodystrophy in neuropathology. However, PMD has been rarely reported from the viewpoints of otology and neurotology.

In PMD, brain MRIs demonstrate dysmyelination and ABR tracings commonly show only waves I and II. It is questioned whether the auditory acuity of children with only waves I and II on their ABR tracings manifest brainstem deafness or not.

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12.2 Case Reports

12.2.1 Patient 1

12.2.1.1 Hearing in a Young Adult with Pelizaeus-Merzbacher Disease

The first patient was a 19-year-old male who had been delivered normally at full term weighing 3526 g. Horizontal nystagmus after birth. At 3 years, his trunk and upper extremities were hypotonic and his lower extremities were spastic. His T2-weighted MRI scans revealed a high signal intensity in the white matter and a low signal intensity in the gray matter of the cerebrum, but there were no abnormal intensities in either area in the cerebellum or in the spinal cord (Fig. 12.1). ABR tracings showed only waves I and II. He could not verbalize but he could hear well enough to enjoy listening to conversation and music at present age. He had a normal hearing threshold by COR (Fig. 12.2) and he had normal speech discrimination during speech audiometry. This complex of symptoms and findings can be explained by a blockage of nerve conduction through dysmyelinated axons or the desynchronization of neurons and nerves in ABR waves following wave I and II (Kaga et al. 2005).

12.2.2 Patients 2 and 3

12.2.2.1 Hearing in Two Children with Pelizaeus–Merzbacher Disease and Whose ABRs Evoked Only Waves I and II

We have followed up two patients with PMD since early childhood. Case 2 is an 11-year-old boy and case 3 is a 15-year-old boy in whom horizontal nystagmus was recognized after birth. Their MRIs showed diffuse dysmyelination of the cerebral white matter. ABR responses included only waves I and II and the absence of all subsequent components. However, their COR audiometric findings indicated thresholds of 20–30 dB HL. Both patients could converse orally and had auditory perception and speech abilities better than those of most of the patients with PMD as reported in the literature.

12.2.3 Patient 4

12.2.3.1 Hearing in a Patient with Classical Pelizaeus–Merzbacher Disease

This patient was a 23-year-old male with a patient with the classic type of PMD (Pelizaeus 1885). He was normal at birth following a normal pregnancy. Nystagmus and head tremor were observed at 2 months of age. Head control and sitting were not achieved. He could crawl around on his elbows at 6 years of age but afterward

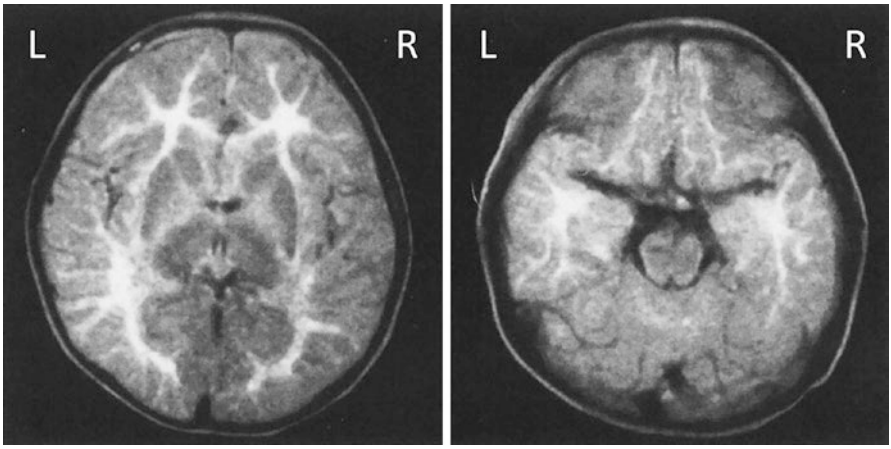

Fig. 12.1 T2-weighted MRI of the brain showing a high-intensity signal in the subcortical area. Reused from Kaga (2009) with permission

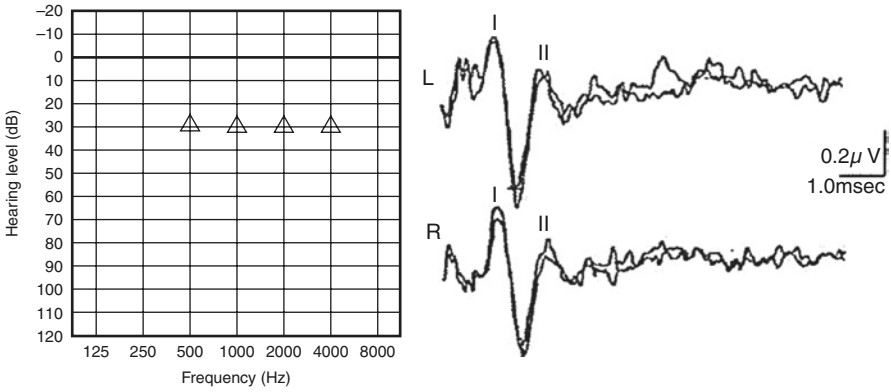

Fig.12.2 (**a**) COR audiometry: normal threshold. (**b**) Auditory brainstem response: Only waves I and II are elicited

he lost even this ability. He showed hyper-reflexia and progressive spasticity of the lower extremities. His verbal IQ (VIQ) as measured by the Wechsler Adult Intelligence Scale (WAIS) was 91. MRI demonstrated high-signal areas in all cerebral white matter with inversion of the usual contrast (Fig. 12.3).

ABRs elicited Wave I but all subsequent components were absent. Pure tone audiometry showed normal thresholds bilaterally. During speech audiometry presented by headphones he gave incorrect responses to monosyllables and his perception of three-syllable words was lost as well. However, his field perceptive ability of both single-syllables and whole words was normal.

He was unable to speak any words because of severe dysarthria. Speech therapy was started at 16 years of age. Education of written language was introduced and at 17 years of age it became possible for this patient to communicate with others using a communication board with letters.

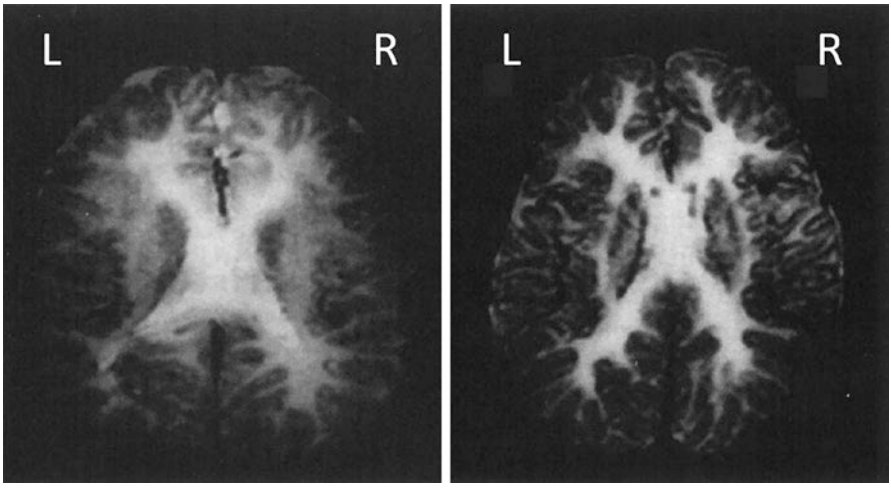

Fig. 12.3 T2-weighted MRI of the brain showing a high-intensity signal in the subcortical area. This patient had normal speech discrimination. Reused from Kaga (2009) with permission

12.3 Discussion

PMD results in white matter dysgenesis of the brain. Most children with PMD require comprehensive nursing care. Their speech and language abilities are poor or even absent. As such, evaluating hearing ability is difficult in children with PMD. However, behavioral audiometry in four children showed responses to sounds with mild or moderate hearing loss.

Our study suggests that early neurophysiological diagnosis, brain MRI and physical rehabilitation are important in order to treat such severely handicapped children from the point of view of enhancing their quality of life.

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Chapter 13
Long-Term Hydrocephalus

Abstract We herein present a patient with auditory agnosia that may provide insight into this condition.

This patient was a 27-year-old female. She was diagnosed with congenital spina bifida and had experienced CSF leakage since birth. Brain CT revealed hydrocephalus immediately after birth and at 4 months of age she underwent her first ventriculoperitoneal (VP) shunt surgery. She lost all hearing in her right ear immediately after surgery and she began to rapidly lose hearing in her left ear about 25 months after the onset of her right ear problems. However, ABRs from both ears were normal.

Keywords Hydrocephalus · Auditory agnosia · Lip-reading

13.1 Introduction

Long-term hydrocephalus due to congenital spina bifida that damaged subcortical auditory structures (Ironside and Pickard 2002). Long-term hydrocephalus is a chronic accumulation of cerebrospinal fluid (CSF) within the ventricles of the brain due to a result of a disturbance of its secretion, absorption, or circulation of CSF and could apply pressure to the brain.

The defining diagnosis between hydrocephalus and cerebral atrophy is necessary but it is somewhat difficult. Cerebral atrophy is sometimes used as synonymous with enlargement of cerebral ventricles mainly the lateral ventricle enlargement. Hydrocephalus is a possible complication of meningitis or other inflammatory diseases in the central nervous system which causes peripheral sensorineural hearing loss.

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13.2 Case Report

13.2.1 Patient

A 27-year-old female who is currently exhibiting auditory agnosia after chronic severe hydrocephalus due to congenital spina bifida. She was diagnosed with congenital spina bifida and had experienced CSF leakage since birth. After years of hydrocephalus, she gradually suffered from hearing loss in her right ear from 19 years of age followed by hearing loss in her left ear (Fig. 13.1). During the time when she retained some ability to hear she experienced severe difficulty in distinguishing verbal sounds (R 0%, L 0%), environmental sounds (oral answer 4%, picture matching answer 75%), and musical instrumental sounds (0%). However, her ABR (Fig. 13.2) and distortion product otoacoustic emissions (DPOAE) were

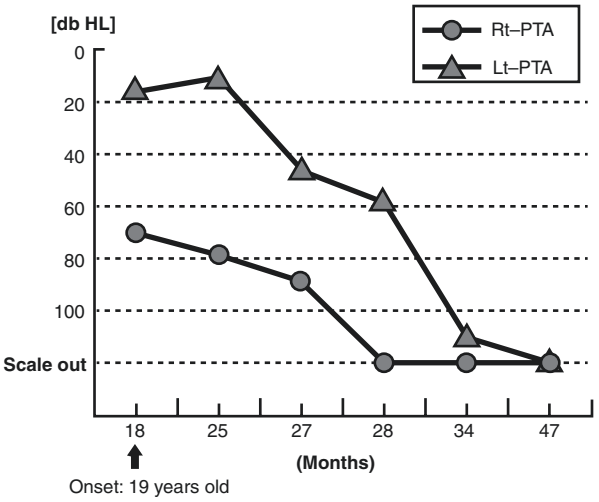

Fig. 13.1 Illustration of pure-tone threshold average changes over time after the onset of hearing problems (calculated by the average thresholds to the frequencies of 250, 500, 1000, and 2000 Hz) (Zhang et al. 2011), copyright ©2011 Acta Oto-Laryngologica AB (Ltd.), reprinted by permission of Taylor & Francis Ltd., http://www.tandfonline.com on behalf of Acta Oto-Laryngologica AB (Ltd.)

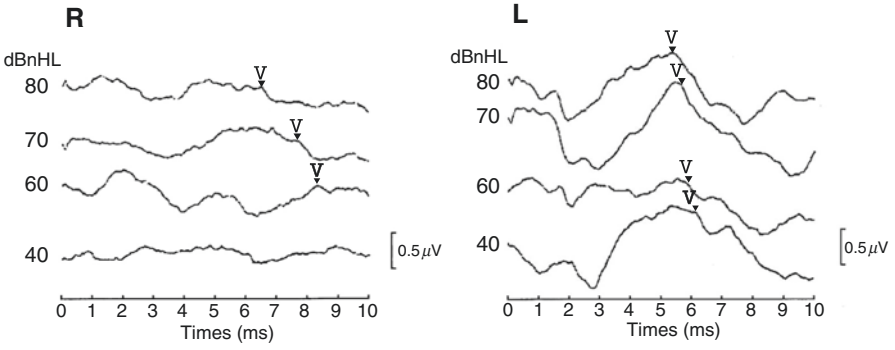

Fig. 13.2 ABRs of the patient 5 years after onset. Waves in the left ear were largely preserved whereas the wave thresholds in the right ear were elevated (Zhang et al. 2011), copyright ©2011 Acta Oto-Laryngologica AB (Ltd.), reprinted by permission of Taylor & Francis Ltd., http://www.tandfonline.com on behalf of Acta Oto-Laryngologica AB (Ltd.)

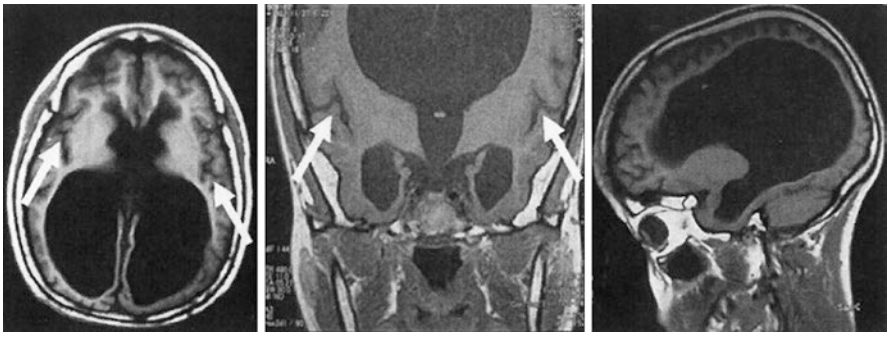

Fig. 13.3 Brain MRI disclosed severe hydrocephalus. The cerebral white matter including bilateral auditory radiations was severely damaged whereas the auditory cortices were intact (arrows) (Zhang et al. 2011), copyright ©2011 Acta Oto-Laryngologica AB (Ltd.), reprinted by permission of Taylor & Francis Ltd., http://www.tandfonline.com on behalf of Acta Oto-Laryngologica AB (Ltd.)

largely intact in the left ear. Her bilateral auditory cortices were preserved, as shown by neuroimaging, whereas her bilateral auditory radiations were severely damaged owing to progressive hydrocephalus (Fig. 13.3). Although she ultimately had a complete bilateral hearing loss she felt pleasure when listening to music. After years of self-training to read lips she regained a fluent ability to communicate. Lip-reading test by 25 three-syllable Japanese words and 10 Japanese short sentences showed 97% correct responses. The clinical manifestations of this woman indicated that auditory agnosia can occur after long-term hydrocephalus due to spina bifida; the secondary auditory pathway or non-specific auditory system may play a role in both auditory perception and hearing rehabilitation (Zhang et al. 2011).

13.3 Discussion

To the best of our knowledge, auditory agnosia caused by long-term severe hydrocephalus due to congenital spina bifida has not been reported. Shivashankar et al. reported two cases of auditory agnosia due to acute hydrocephalus subsequent to the obstruction of the CSF circulation pathway by the third cerebral ventricle tumor (Shivashankar et al. 2001). The two patients demonstrated typical pure word deafness and communication problems. However, they regained hearing perception after radiotherapy and the release of the blockage. What is different in the present case is that auditory agnosia occurred after 19 years of hydrocephalus. Over this long period of time, the white matter of the patient's brain had been gradually damaged and hearing was lost permanently. When the bilateral auditory pathways were finally interrupted, auditory agnosia occurred.

There are two auditory pathways in the human brain, the primary (specific) auditory pathway and the secondary (nonspecific) auditory pathway (Guyton and Hall 2000). The primary auditory pathway has been studied thoroughly; however, much

remains unknown about the secondary auditory pathway and its relationship to the primary pathway.

In conclusion, the above patient demonstrated that auditory agnosia can be induced by chronic hydrocephalus due to congenital spina bifida.

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Chapter 14
Brain Malformation and Hydrocephalus

Abstract There are several types of brain anomalies. It is an important issue with respect to auditory function whether children with brain anomaly but with a preserved brainstem and thalamus are able to hear. If they can hear certain sounds how can this pathophysiology be understood?

Two infants with hydranencephaly were analyzed using brain MRI and ABR. Ages of the two infants were a 3-month-old male and a 3-year-old male.

Keywords Hydrocephalus · Hydranencephaly · ABR · Cerebral cortex · Brainstem

14.1 Introduction

Hydranencephaly, first described by Crueilhar, is a rare and severe anomaly of the central nervous system in infants whose entire cerebral hemispheres are nearly destroyed due to vascular disturbances (Hamby et al. 1950; Halsey et al. 1971). A fluid-filled membranous sac resembling a large cyst largely replaces the brain (Hanigan et al. 1988). The cause of hydranencephaly is considered to be an occlusive disease of the supraclinoid part of the internal carotid artery (Mori et al. 1995), which occurs any time between the third month of gestation and the second postnatal year.

An infant with hydranencephaly and another infant with severe hydrocephalus were examined by brain MRI, ABR, and behavioral observation audiometry (BOA). The question is whether such infants can respond to auditory stimuli. If they can, is it startle reflex or conditioned reflex?

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https://doi.org/10.1007/978-981-10-1479-6_14

14.2 Case Reports

14.2.1 Patient 1

This patient, a 3-month-old male, was born after 40 weeks of gestation with no apparent complications during labor or delivery. The Apgar score was 10, and the sucking and Moro reflexes were slightly depressed. His weight at birth was 3.4 kg, head circumference 37 cm, and height 53 cm. His head grew extremely large and the sunset phenomenon occurred very often.

MRI of the brain revealed that the patient had a brainstem, cerebellum, and thalamus but otherwise had only membranous sacs containing cerebrospinal fluid (Fig. 14.1). These findings indicated a rare form of hydranencephaly, namely hydrocephalus, which is associated with severe brain malformations.

BOA showed responses at 90–100 dB HL. ABRs showed normal waveforms for both ears at loud click intensities and a mild threshold elevation at 70 dB HL (Fig. 14.2). In addition, auditory evoked middle latencies and slow vertex responses were absent in both ears.

14.2.2 Patient 2

A 3-year-old boy with quadriplegia and auditory visual impairment. He was born at 26 weeks and 3 days. His birth weight was 625 g. After a bacterial sepsis, he

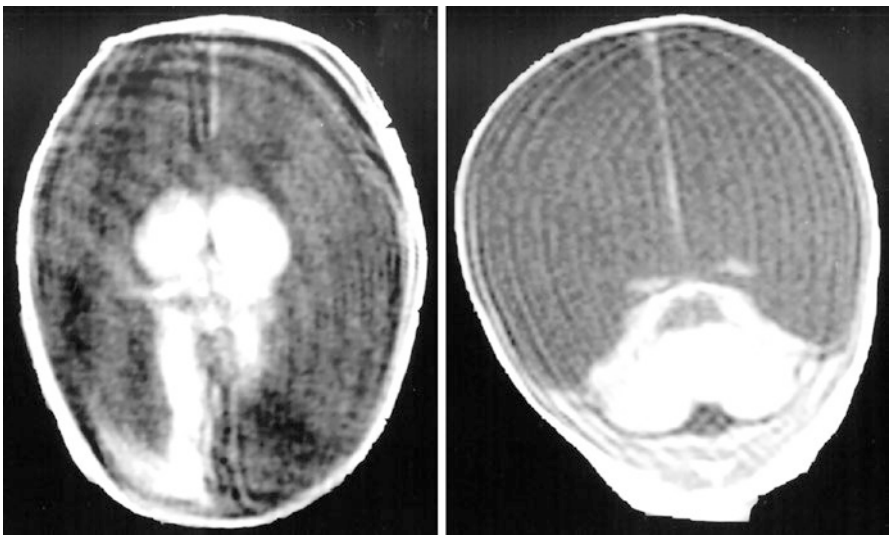

Fig. 14.1 Brain MRI of Case 1 showing the absence of bilateral hemispheres (Kaga et al. 2002), copyright ©2002 Acta Oto-Laryngologica AB (Ltd.), reprinted by permission of Taylor & Francis Ltd., http://www.tandfonline.com on behalf of Acta Oto-Laryngologica AB (Ltd.)

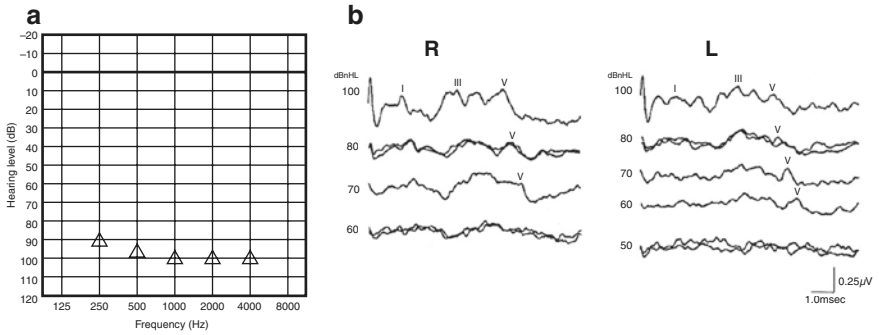

Fig. 14.2 (**a**) BOA, (**b**) ABRs of Case 1 at 3 months (Kaga et al. 2002), copyright ©2002 Acta Oto-Laryngologica AB (Ltd.), reprinted by permission of Taylor & Francis Ltd., http://www.tandfonline.com on behalf of Acta Oto-Laryngologica AB (Ltd.)

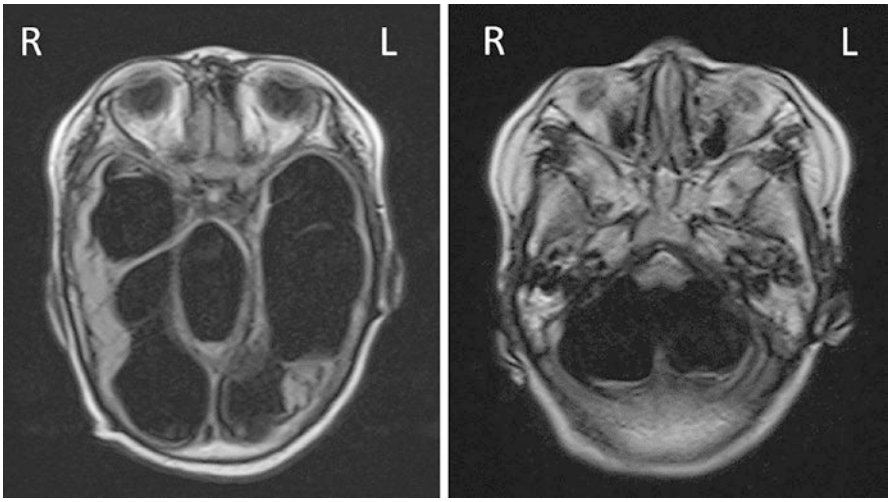

Fig. 14.3 Brain MRI of Case 2. Bilateral cerebral hemispheres and cerebellum, which contain numerous cysts, are almost entirely replaced by cerebrospinal fluid (Shinagawa and Kaga 2019)

manifested quadriplegia, auditory visual disturbance, and mental retardation. Brain MRI demonstrated severe hydrocephalus with hypogenesis of bilateral frontal, temporal, parietal, and occipital lobes (Fig. 14.3). He reacted to loud noise with a startle reflex, a flashing light, and optokinetic nystagmus (OKN) stimulation. At his age of 1 year, his BOA showed severe threshold elevation (Fig. 14.4a). Objective audiometry demonstrated normal DOPAEs (Fig. 14.4b) and wave I only of the ABR (Fig. 14.5) was near normal thresholds of 40 dB in the right ear and 50 dB in the left ear (Shinagawa and Kaga 2019).

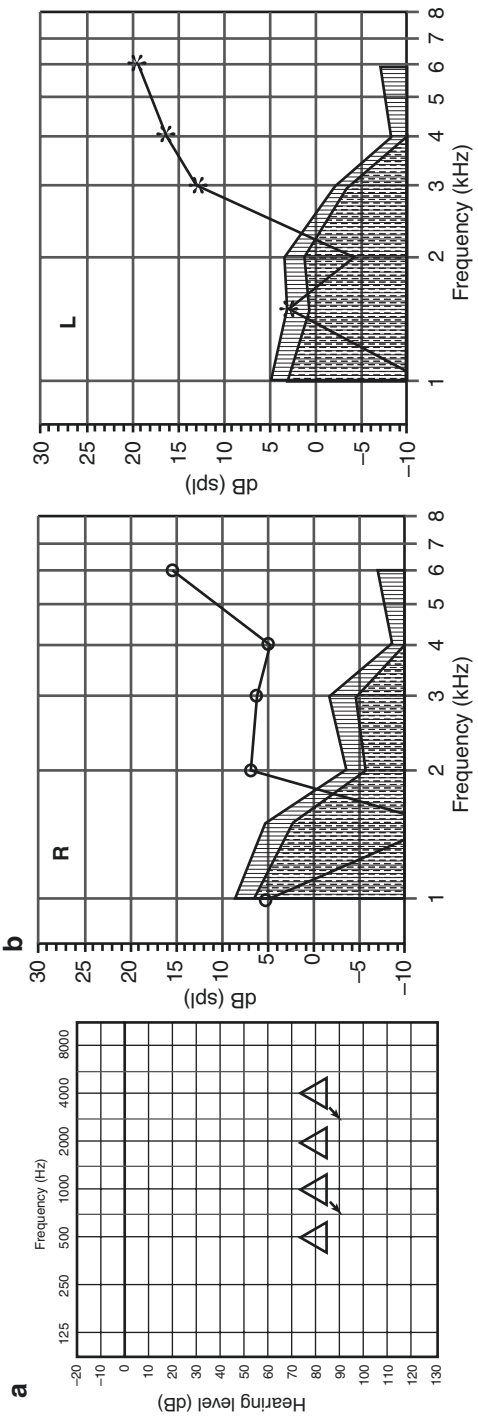

Fig. 14.4 (**a**) BOA of Case 2 at 1 year, (**b**) DPOAE (Shinagawa and Kaga 2019)

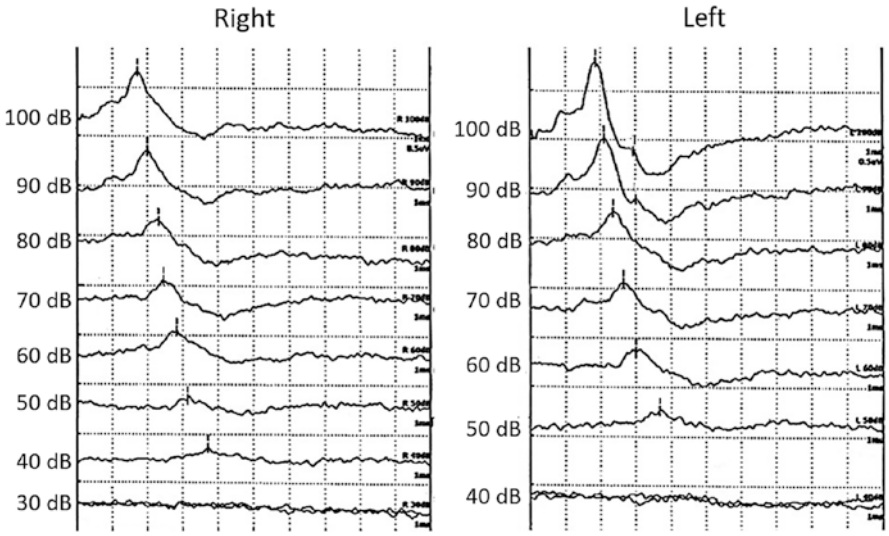

Fig. 14.5 ABRs at 1 year (Shinagawa and Kaga 2019)

14.3 Discussion

These two cases were assessed by BOA which is generally qualitative and not quantitative because of severe mental retardation due to the underlying brain anomalies. The brainstems of these patients were determined, by MRI, to have a normal shape and, by means of ABR, to have a normal peripheral auditory function. The differences in thresholds observed by BOA and ABR suggest differences in the level of auditory development. The startle reflex consisted of a generalized flexion response. The startle reflex was most prominent around the face, neck, and shoulders and less marked in the lower half of the body. The minimum response, with the exception of blinking of the eyes, was in the response of the sternocleidomastoid muscle. This sternocleidomastoid response was often the last component of the generalized startle reflex to disappear with repeated presentation of a stimulus because of habituation. The overall pattern of muscle recruitment in the physiological startle response to auditory stimulation suggests that in humans, as in animals, the auditory startle response originates in the caudal brainstem propagating rostrally from the 7th to the 5th cranial nerve nucleus. The ABR is useful not only for objective evaluation of peripheral hearing acuity and brainstem maturity but also for identifying sites of lesions and reductions in the brainstem function. Moreover, the ABR is very important for determining normal peripheral and brainstem auditory function (Shinagawa and Kaga 2019; Kaga et al. 2002).

In conclusion, our case study reveals that apparent auditory response behavior can be observed using ABR as long as the brainstem is preserved.

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