Pleiotrophy in Coffin-Lowry Syndrome: Drop Attacks, Staphyloma, Hearing Deficit and Premature Loss of Primary Teeth

Yu-Ming Chuang, Shang-Yeong Kwan[1], Jiing-Feng Lirng

Abstract- A 20-year-old male had full manifestation of Coffin-Lowry syndrome and 6 year history of progressively severe drop episodes. His drop episodes were precipitated by unexpected sudden auditory stimuli, and were not associated with electroencephalographical changes. The positron emission tomography disclosed metabolic reduction over bilateral temporal-parietal cortex which could contribute to his exaggerated startle reaction .His drop attack was abolished by clonazepam suggesting that GABAnergic pathway might participate in the neuronal circuit of startle reaction. Thus, we suggest that cortical hypometabolism and GABAergic system play a critical role in the pathophysiology of drop episode of Coffin-Lowry syndrome and that early introduction of clonazepam may prevent further injury and restore his ambulatory capacity.

Retrospectively, early signs of Coffin-Lowry syndrome could be a premature loss of primary teeth and myopia. His premature loss of exfoliative tooth occurred at 7 years of age but was misdiagnosed. Besides, myopia could be another early sign of Coffin-Lowry syndrome which be developed at 10 years of age. Both myopia-associated staphyloma and reduced teeth number could be identified in the cerebral magnetic resonance imaging (MRI) and the plain skull film. Suggesting the important role of cerebral imaging study in the diagnosis of Coffin-Lowry syndrome.

Key Words: Coffin-Lowry syndrome, Drop episode, Premature teeth loss, Staphyloma

Acta Neurol Taiwan 2002:11;18-23

INTRODUCTION

Coffin-Lowry syndrome (CLS) was first independently reported by Coffin et al, and Lowry et al and was recognized as a disease entity by Temtany et al[1,2]. It is transmitted by an X-linked semidominant inheritance. The gene for Coffin-Lowry syndrome is ribosomal S6 kinase 2 (RSK-2), a member of the growth-factor-regulated protein kinase family[3]. Patients with CLS usually have moderate to severe mental retardation and other features such as a dysmorphic face, puffy proximal digits, thick fingers with tapered ends, hypotonia, and hyperextensibility of joints.

Unlike other malformation syndromes which are obvious at birth, the diagnosis of CLS is often established late, after the appearance of skeletal deformities. We examine a male patient with CLS who manifested clinical features and drop episodes that were precipitat-

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Received September 6, 2001. Revised October 22, 2001. Accepted December 11, 2001.
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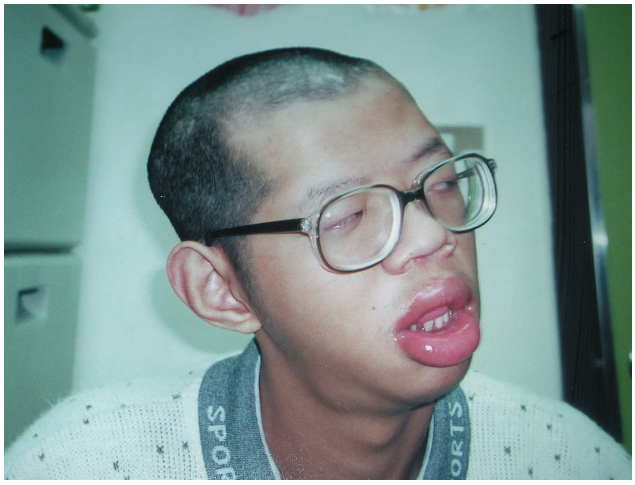

Fig 1. Patient aged 20 years demonstrated dysmorphic, coarse facial features and hypertelorism.

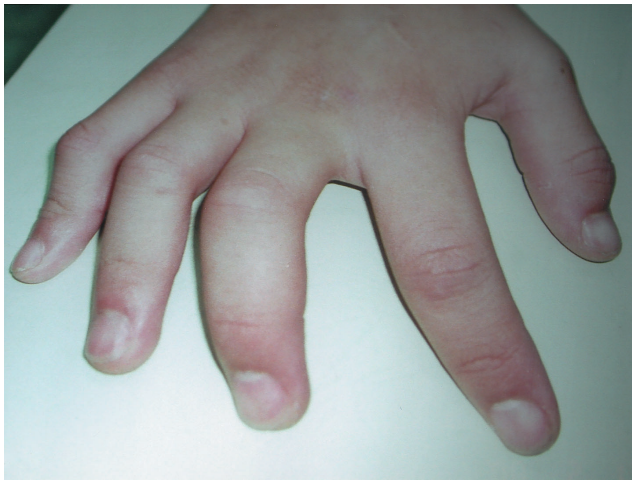

Fig 2. Patient's hands showing fleshy appearances with distinct tapering of the fingers.

ed by sudden auditory stimuli. His stimulus-sensitive drop attacks might belong to the group of pathologically exaggerated startle responses, including startle epilepsy, hyperekplexia, and uncategorized abnormal startle responses. Although these startle responses are clinically unrelated, they share the rapid contraction of certain muscle groups and similar neuronal circuit[4]. This report discusses the mechanisms of his drop episodes and the association with Coffin-Lowry syndrome.

This patient had pleomorphism of clinical manifestations, including premature exfoliative loss of primary teeth, sensorineural hearing loss and staphyloma. Those features were rare in Coffin-Lowry syndrome.

CASE REPORT

The patient, a 20-year-old male, was born at 38 weeks of gestation as a small-for-date infant of unrelated healthy parents. He was developmentally retarded: sitting at 18 months; making no meaningful sounds until age of 3 years; walking at 4 years; speaking words at 4 years and 6 months. He was first brought to our hospital with chief complaint of premature loss of exfoliated primary teeth at 7 years, and a recent loss of both mandibular primary central incisors and maxillary right central primary incisor. Later, he had progressive skeletal deformity as scoliosis since 8 years of age. He was put in residential care for the moderately to severely retarded from 10 years of age, at which time he had limited speech of only two or three words, and severe learning deficit. He was found to have severe myopia. At age of 14 years, he began to have episodes of falling backwards that were induced by unexpected tactile or auditory stimuli. The frequency and severity of these drop attacks worsened with age, and was correlated with a further progression of muscle wasting and thoracolumbar scoliosis. Avoidance of frequent drop attacks became the major concern of his caregiver. Therefore, severe disability was resulted from both his frequent drop attacks and further progression of thoracolumbar kypho scoliosis Reflex epilepsy manifested as atonic seizure was diagnosed. A volproic acid was not effective in abolishing further drop episodes. When he was admitted to our hospital, his height was 160cm and his mental age was about 3 years. He was confined to the chair and his motor skills were clumsy. His face was dysmorphic with hypertelorism, downward slant, flat nasal bridge, prominent forehead, and thick and everted lips (Fig. 1). The face was long with prominent ears. His fingers were fat, puffy, and tapered (Fig. 2). The arche of the foot was flat, and his second and third toes were equal in length. The remaining teeth were irregular (Fig. 3). Neurological examination revealed crucial hypotonia and ataxic gait with stooped posture. Ophthalmologic studies showed severe

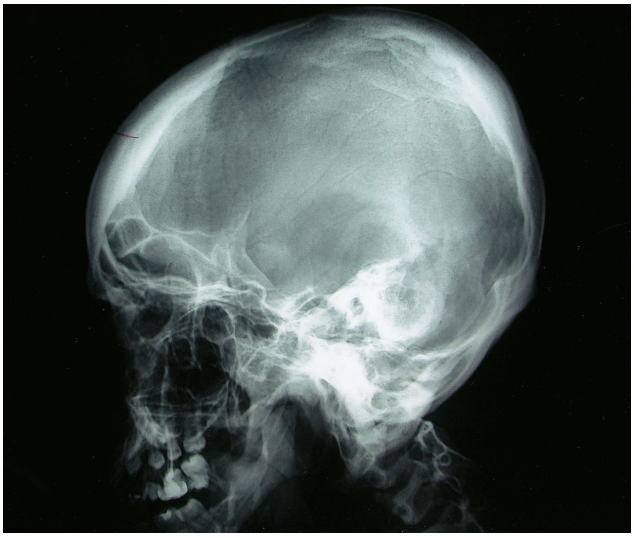

Fig 3. X-ray skull showing irregular remaining teeth with reduced numbers, microcrania, frontal bone thickening, and hyperostosis frontalis interna.

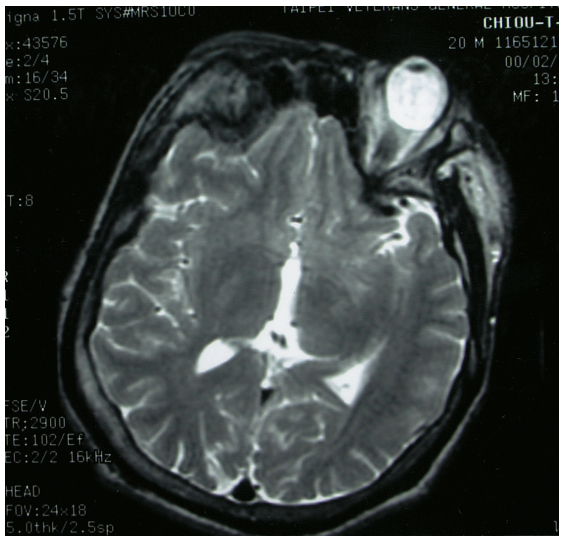

Fig 4. T2-weighted MRI(TR/TE:4000/105) showing bilateral staphyloma.

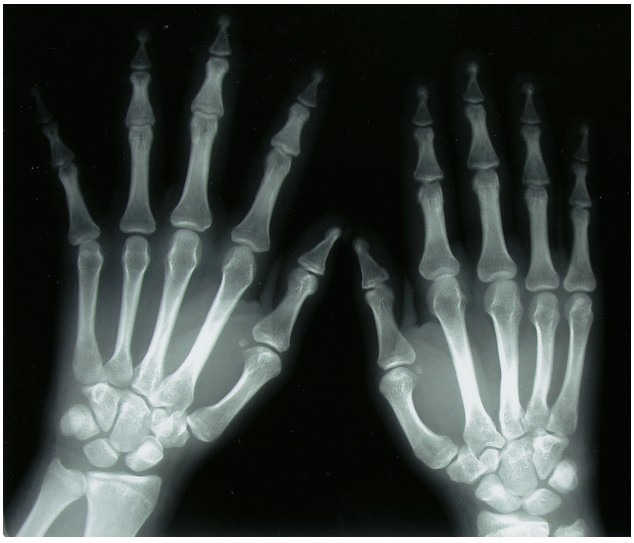

Fig 5. Radiography of the hands showing short distal phalanges with drumstick-shaped terminal phalanges.

bilateral myopia. His myopia was associated posterior staphyloma as disclosed by cranial MRI (Fig. 4). Audiological tests including brain stem evoked potential and behavioral audiogram revealed profound bilateral hearing impairment (right side 85dB loss, left side 105dB loss). Poor pneumatization of mastoid cells was disclosed by MRI scan of the temporal bones. The radiological examinations revealed a drumstick distal phalanges (Fig. 5). The spines were markedly abnormal with lumbar scoliosis. The vertebral bodies were abnormal with a concave anterior aspect and a deficiency in the epiphyseal ring. The end plates were irregular which correlated with changes. The like Scheuermann's disease skull showed microcrania, relative frontal bone thickening, maxillary hypoplasia and the irregular remaining teeth which had a abnormal enlarged pulp chamber (Fig. 3). Positron emission tomography (PET) disclosed diffuse cortical hypoperfusion including mesial temporal lobe (Fig. 6).

Clonazepam was introduced at a dose of 0.5mg and gradually increased to a total daily dose of 3mg. The patient experienced dramatic improvement of the symptoms.

The 16-channel-telemetric digital video-EEG monitoring during the drop attacks showed interictal diffuse background slowing at theta range and ictal changes consisting of subtle brief bursts of activities of high voltage 2-3Hz delta and medium voltage 4-6 Hz theta intermingled with a few low to medium voltage sharp waves maximally at bilateral centro-parietal regions lasting for 1 second (Fig. 7). EEG also showed several consecutive startle responses induced by tactile stimuli accompanied by high voltage localized to the parietal-occipital

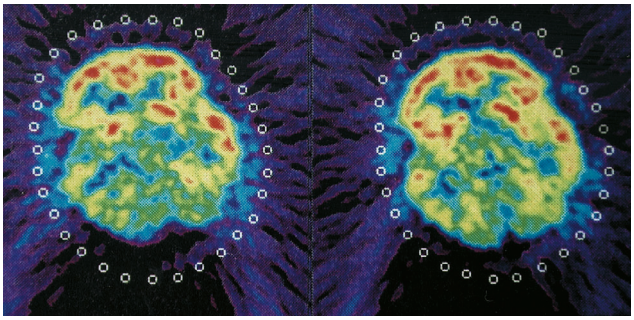

Fig 6. PET showing diffuse cortical hypoperfusion including mesial temporal lobe.

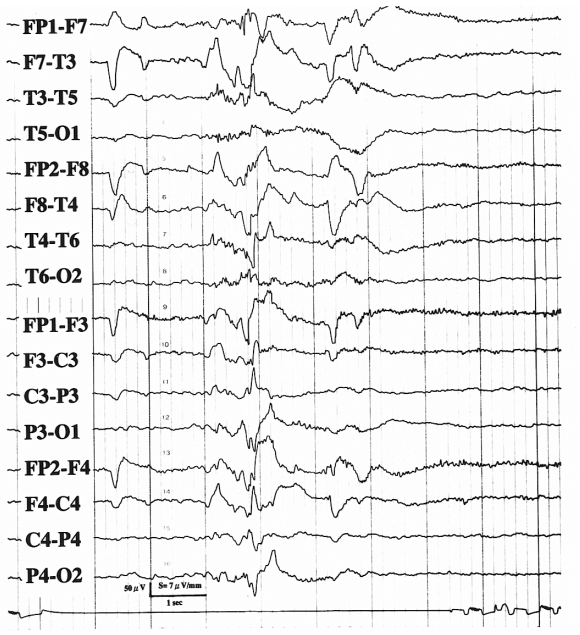

Fig 7. Ictal EEG showing brief subtle bursts of activities consisting of mixed frequencies of mainly high voltage 2-3Hz delta and medium voltage 4-6 Hz theta activity intermingled with a few low to medium voltage sharp waves maximally at bilateral centro-parietal regions lasting for 1 second.

regions. The subject received a total of 32 startle stimuli within one test session of 2 hours. including 16 auditory stimuli by 110dB stimuli (8 stimuli at right side and the other at left side), 8 somatosensory stimuli by tapping on the sternum with a neurological hammer, and 8 flash light stimuli. In every kind of stimulus, they lacked significant habituation even 5 to 7 trials. No epileptic discharges were noted on repeated 24 hours EEG monitoring.

DISCUSSION

Early diagnosis of CLS is not easy. Premature exfoliated teeth loss had been reported to be one of the early signs of CLS[5]. Premature exfoliated primary teeth loss at 7 years of age was the first clue for our patient but the diagnosis was missed. Other unique oral manifestations of CLS include microdontia, especially of the anterior teeth, spacing between teeth, delayed eruption of teeth, hypodontia and mandibular prognathism. Usually, oral manifestations may preceed muscle-skeletal manifestations.

Drop episodes had been well described in CLS with electrophysiological studies. Although the attack has been thought to be an exaggerated startle response, pathophysiology of this phenomenon is debated[6]. The startle syndrome can be provoked by diverse unexpected sensory stimuli including auditory, somaesthetic, and even visual stimuli. Startle syndrome associated drop attack can also be caused by a variety of conditions including pathological exaggeration of normal startle reflex, reflex epilepsy, brainstem reticular reflex myoclonus, and other unknown conditions. EEG is a poor method to verify the etiology while, in fact, pathologically exaggearted startle response is difficult to be differentiated from the reflex epilepsy such as atonic seizure clinically and eletrcophysiologically, and ictal video-EEG only demonstrated nonspecific short duration bilateral synchronous high voltage delta and theta burst and preserved consciousness could occur in both reflex -atonic seizure and exaggerated startle response. However, verification of the startle of the disease entity syndrome has therapeutic implications especially in the choice of medication. Exaggerated startle response responds to clonazepam while reflex epilepsy usually to other antiepileptic agents.

In this case, the diagnosis of exaggerated startle reaction was based on the following reasons (1) Niether ictal EEG nor interictal EEG showed epileptiform discharges, (2) There was no MRI evidence of focal lesion consistent with the possibility of reflex epilepsy, and (3) Atonic seizure rarely exists independently of the Lennox-Gastaut syndrome.

Startle syndromes share a common pathway of neur-

al circuit which is generated in the pontine reticularis caudalis nucleus and is modulated by hemispheric structures[4]. Afferent inputs may be relayed subcortically or cortically to activate this bulbopontine reflex system, with variable afferent delays. Therefore either cortical or subcortical lesion might attribute the occurrence of exaggerated startle response[4]. However, PET of our patient showed hypometabolism in the parietotemporal and visual cortex with spearing of cerebellum and subcortical structures, is similar to the pattern of PET findings in Alzheimer's disease. Furthermore, a significant hypometabolism of bilateral mesial temporal structures including amygadala was also noted The hypometabolism of temporal-parietal and visual cortex might contribute to his exaggerated startle reaction which is evoked by either afferent inputs or the modulation of efferent pathway at hemisphere level.

With respect to the dramatic effect of clonazepam there was only one reported case[6]. However, startle epilepsy can also respond to clonazepam due to its antiepileptic entity.

Our patient had latent severe sensori-neural hearing loss. Sensori-neural hearing loss has also been reported to be in patients with CLS and is correctable by hearing aid[9]. Thus, behavioral audiogram or electrophysiology test as brain stem.

Finally, there is MRI evidence of bilateral staphyloma which is thought to be myopia related. Myopia with staphyloma indicates a sclera architectural abnormality, which may be seen in many collagen fiber diseases. The pathological change was a damage of thin sclera with a loss of normal rhombic collagenous alignment, causing loss of eyeball rigidity and flexibility against changes[10]. CLS is reported to represent a metabolic abnormality in collagen proteoglycan which may caused by a mutation in gene coding RSK2, a growth factor regulated protein kinase[11]. Metabolic abnormality in collagen in CLS can be responsible for many aspects of its connective tissue manifestations.

Staphyloma associated with myopia has never been reported in patient with CLS. Our case suggests that ophthalmogist can play a vital role in limiting the vision loss and improve the learning disability.

Interestingly, exaggerated audiogenic startle reflex occurred in our patient even though he had severe bilateral hearing deficit. Similarly, exaggerated videogenic startle reflex occurred even he had visual acuity deficit (severe myopia with staphyloma). Acoustic afferent inputs travel to dorsal cochlear nucleus which has been shown to projection to the nucleus reticularis pontis caudalis to elicite startle in rats[12].

In conclusion, we would like to stress the importance of an early recognition of early signs of CLS. These include premature loss of primary teeth, myopia, and sensori-neural hearing loss. Early diagnosis may lead to early identification of the correctable sensorineural hearing loss and myopia. Furthermore, clonazepam appeared to be effective in controlling drop attacks.

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