Postural and Gait Abnormality in Even Plus Syndrome

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Abstract

Five cases of Even-Plus syndrome have been reported, 2 in the year 19991 and 3 in the year 20152. We recently diagnosed another female patient with Even-Plus syndrome with a postural and gait abnormality. Left patellar dislocation was identified and corrected in order to limit patient’s disability.

Keywords: Even-Plus syndrome; Hypoplasia; Pediatrics; Radiology; Mutation

Introduction

The name Even-Plus syndrome came from abnormal findings of the epiphysial, vertebral, ear, nose, plus associated findings. So far, 5 patients namely 2 (siblings) from Chile, 1 from Korea, and the other 2 (siblings) from Algeria have been identified to have this syndrome. This case reports the sixth patient from Indonesia. A mutation of the HSP9 gene has been identified in all these patients. The heat-shock 70 kDa protein 9 or the HSPA9 gene is known to be responsible in coding mitochondrial chaperones to assist in protein folding eventually involved in the control of cell proliferation and inhibition of apoptosis [1,2].

Many studies have focused on finding out the other roles of heat shock proteins. There has been evidence that HSPA9 which is a part of the HSP70 family member is also found in extra-mitochondrial sites which include the endoplasmic reticulum, cytoplasmic vesicles and cytosol [3]. In addition, a number of animal studies have proven that HSPA9 has been related to embryogenesis [4-6]. In mice embryo, HSP70 expression has been found in the post-implantation phase. In addition to its role in embryogenesis, heat shock proteins have been found to also affect cell movements, proliferation, morphogenesis and apoptosis in the absence of stress [7]. There is still no definitive treatment for this syndrome, therefore, this paper aims to report a patient’s management which was intended to limit patient’s disability.

Case Presentation

A 7-year-old female who presented with an abnormal posture and gait in the last 1 year before referral to our hospital. Mother mentions that patient always had an awkward posture and delayed motoric skills since young. Patient still attends school and performs low impact physical activities daily. She is still able to walk and run over short distances. Patient stabilizes herself by bending her upper body forward and swinging her arms when stepping forward. However, over the last 6 months, patient’s posture began to worsen in a forward bend and her walking abilities started regressing. Mother realized that the “ball” which is normally in the center of her knee, began to displace laterally to the side of the knee. The attending doctor mentioned that the only abnormality seen was microtia. Patient’s hearing examination revealed normal results.

Patient’s physical examination showed midface hypoplasia, microtia, high arched palate, short neck, synophrys, hypoplastic nose, lateral hair whorls, tight hamstring, leg length discrepancy, dislocated left patella, kyphosis, and scoliosis (Figure 1). The neurological physical examination revealed limited neck range movement on all sides. Normal physiological reflexes on both upper and lower extremities.
Muscular strength of the upper extremities and right lower extremity were 4/5. The muscular strength of the left lower extremity was 3/5. Patient’s abnormal gait had been captured in still pictures (Figure 2). The figure shows the abnormal bilateral arm swinging movement and a forward body bend every time patient’s right leg steps forward.

A bone survey was performed revealing metaphyseal dysplasia and multiple vertebral cleft from her cervical down to the lumbar region (Figure 3). A cerebral MRI was performed which did not reveal any soft tissue abnormalities, however, there was atlanto-axial joint dysplasia (Figure 4). A Knee MRI revealed an epimethaphyseal dysplasia of the distal femur and a dislocated patella to the lateral side, a posterior subluxation of the tibia, dysplasia of the medial meniscus, a tear in the lateral meniscus and the anterior cruciate ligament (Figure 5). An electromyography study was also performed and excluded any lower motor neuron or muscle involvement. A somatosensory evoked potential test was also performed and revealed no abnormalities. From a multi-disciplinary discussion with the department of pediatrics, orthopedics, medical rehabilitation and radiology, it was concluded that patient should be refrained from walking and should only move around using a tricycle to help strengthen her hamstrings. A corrective surgery was not carried out immediately as it would impact on patient’s vertical growth. Patient was under supervision and was monitored monthly.

A 2-month observation showed that patient had a worsening kyphosis, scoliosis and gait, i.e., patient was unable to run and was having difficulty to walk independently. Therefore, a corrective surgery to relocate the left patella was conducted to limit any further disability. Post corrective surgery, patient underwent medical rehabilitation to release the hamstring tightness and correct her posture (Figure 6). Figure 7 shows patient’s gait 3 months post corrective surgery. Patient is walking stably with no bilateral arm swing and can maintain an upright posture with the help of a left knee brace. Future for patient includes an outer ear surgery to correct patient’s microtia as well as regular post-corrective follow ups on the location of the left patella. Our orthopedist assumes that there needs to be several more surgeries to maintain the location of the patella until patient reaches her final height.

**Laboratory Studies**
Next generation sequencing of an exome panel on a S5 Ion Torrent machine revealed two HSPA9 mutations, both at the heterozygous state: The missense mutation c.446A>T, p.Asn149Ile in exon 5, and the stop mutation, c.1687A>T, p.Lys563Ter, in exon 14. Both mutations were confirmed by Sanger sequencing.

Discussion

The diagnosis of the Even-Plus syndrome in our patient was first made by entering all dysmorphic findings into the Online Mendelian Inheritance in Man (OMIM) search. Compared to the 5 cases that were previously reported, our case had similar facial features and bone abnormalities, especially epiphyseal dysplasia. One patient was reported to also have a laterally dislocated patella, like this case [2].

The 2 previous case series did not report the details regarding patients’ management. The summary of clinical features of 2 patients with EVE syndrome which have very similar clinical characteristics as Even-Plus syndrome, however have not undergone genetic diagnostic procedures and 4 patients with confirmed Even-Plus syndrome (Table 1). The clinical features of patients 1 and 2 were adopted from Amiel et al. patients 3, 4 and 5 were adopted from Royer-Bertrand et al. [1,2]. The youngest age that a patient was referred for diagnosis to the genetics unit was 4 months old due to facial dysmorphism and due to a family history of her sister aged 3 years 9 months having similar features. This patient had facial dysmorphism since birth but was failed to be highlighted. In addition, striking gait and postural abnormalities only began at 6 years old, hence, patient was referred to our hospital for further examinations at the age of 7 years old.

The abnormal gait in this patient could be due to several factors, i.e., the patellar dislocation, the atlanto-axial dysplasia, the leg length discrepancy that was due to the tight hamstring, the medial and lateral meniscus tear as well as the distal femur dysplasia. From patient’s history, mother mentions that worsening of patient’s posture coincided with the patellar displacement. Also, it was concluded that the leg length discrepancy was due to the tight hamstrings that were due to a compensatory mechanism of the femur dysplasia as well as the patellar displacement. Neurologic involvement was excluded based on the somatosensory evoked potential and the electromyography results.

Figure 6: Post-operative. a. Bilateral knee brace, b. Rehabilitative procedures to release tightness on hamstring.

Figure 7: Patients gait 3 months post corrective surgery.
In addition, intraoperatively, it was concluded that the meniscal tears did not cause any mechanical blocks, therefore, only the patellar dislocation was corrected. Clinically, patient’s posture as well as walking ability have improved significantly (Figures 7 and 8). There was no more bilateral arm swinging as well as forward body bend when patient walks with her knee braces.

This patient still underwent a corrective surgery despite knowing that a few more upcoming surgeries is for certain due to her growing height. The surgery was aimed to limit patient’s disability, i.e., a worsening epiphyseal plate on the patellar region and to limit the over-compensation of patient’s backbone that has caused severe scoliosis and kyphosis. Patient is undergoing routine physical rehabilitation to restore femur and back strength. She will also be monitored physically and radiologically every 6 months as patient does not live in Jakarta.

**Conclusion**

A 7-year-old female patient with Even-Plus syndrome had undergone surgical and rehabilitative measures to manage her

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| Features                              | Patient 1                | Patient 2                | Patient 3                | Patient 4                | Patient 5                | Current patient          |
|---------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Origin                                | Algeria                  | Algeria                  | Korea                    | Chile                    | Chile                    | Indonesia                |
| Birth measurements                     | Length 46.5 cm, weight 2.58 kg (term delivery) | Length 43 cm, weight 2.5 kg | Length 38 cm, weight 2.2 kg (at week 39) | Length 39 cm, weight 2.8 kg (at week 38) | Length 39 cm, weight 2750 g (at week 38) | Length 49 cm, weight 3.5 kg (at week 38) |
| Musculoskeletal (Epiphyseal abnormalities) | Spontaneously dislocate her elbows. At age 4.5 months old absence of epiphyseal ossification, irregular metaphysis of the femoral bone | Lumbar spine rigidity, history of the ability to dislocate eibo. Microepiphyses of femoral heads, metaphyseal widening, short femoral neck. Irregular metaphyses of the knees. | Dysplastic femoral heads at birth and showing bilateral femur and marked dysplastic distal femoral epiphyses at 4 years. | Underossified pubic bones, at birth, bilateral dysplasia of the femoral heads hip dislocation. At 5 years: "Bifid" appearance of distal femur with dysplastic epiphyses, laterally dislocated patella | No data | No data |
| Vertebrae                             | Midcoronal vertebral clefts | Midcoronal vertebral clefts | No data | No data | Remnants of coronal clefts of the vertebral bodies. | Severe scoliosis and kyphosis. Multiple vertebral clefts and atlanto-axial dysplasia. |
| Ears                                  | Dysplastic with hypoplastic helices and antihelices | Dysplastic ears | Absent external ears (anotia), open ear duct | Severe microtia with absent upper helix | Absent external ears with open ear duct, possible hypoacusitis | Severe microtia |
| Nose                                  | Depressed nasal bridge, short nose with anteverted nares | Depressed nasal bridge | Hypoplastic nose with vertical groove on tip (bifid tip) and triangular nares | Hypoplastic nose with vertical groove on tip (bifid tip) and triangular nares | Hypoplastic nose with vertical groove on tip (bifid tip) and triangular nares | Hypoplastic nose with vertical groove on tip (bifid tip) and triangular nares |
| Eyes                                  | No cataract | No cataract | Synophrys, no cataract | Synophrys, no cataract | Synophrys, no cataract | Synophrys, no cataract |
| Teeth                                 | No data | Normal | No data | No data | Single upper central incisor, absence of some lateral incisors | Normal |
| Skin                                  | No data | Unilateral patch of skin aplasia above the ear | Atopic dermatitis, sparse hair | Two lateral hair whorls and area of aplasia cuts on the skull vertex | Area of aplasia cuts on skull vertex | Two lateral hair whorls. No areas of aplasia cuts |
| Heart                                 | Normal echocardiography | Normal echocardiography | ASD (spontaneously closed at age 20 months) | ASD (ostium secundum) | Patent foramen ovale and aneurysmal septum | Normal echocardiography |
| Gastrointestinal                      | No data | No data | Anal atresia | Normal abdominal ultrasoundography | Anal atresia | Normal abdominal ultrasoundography |
| Kidney/urogenital                     | Normal ultrasound | Normal ultrasound | No abnormalities on ultrasound | 1 UTI at 1 year but normal renal ultrasoundography | Vesicoureteral reflux | Hypoplastic bilateral kidneys with normal kidney functions |
| Brain                                 | No data | No data | Normal MRI at age 5 months | Normal cerebral ultrasoundography | Agenesia of the corpus callosum with separated frontal horns | Normal brain MRI with dysplasia of atlanto-axial joint |
| Psychomotor development               | Normal | Normal | Borderline-normal | Normal evaluation at kindergarten level, including language | Moderate developmental delay | Borderline-normal |
| HSAP9 mutations                       | Has not been performed | Has not been performed | p.Y128C/p.V296* | pR126W/p.R126W | pR126W/p.R126W | Compound heterozygous for the missense mutation c.446A>T, p.Asn149Ile in exon 5 and the stop mutation, c.1687A>T, p.Lys563Ter, in exon 14. |

**Table 1**: Summary of the clinical features of 6 patients with Even-Plus Syndrome.
abnormal gait which resulted in her abnormal posture. There were risks and benefits to be considered in this case, the risk being that patient must undergo follow up surgical procedures as she has not reached her potential height. The benefits that were considered to carry on with the surgical procedure was to limit patient’s postural abnormality which was severe scoliosis and kyphosis.

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