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Case Report Open Access

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 epiphyseal, 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 HSPA9 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 at that time, suggested physiotherapy. Patient underwent multiple physiotherapy sessions for 4 months with no improvements. Patient was then referred to our hospital with the diagnosis of "suspected syndrome".

Patient was born to non-consanguineous parents after 5-years of infertility, there were no known external efforts to conceive such as drinking herbal medications or *in-vitro* fertilization. There was also no significant past as well as family history. After patient was born, 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.

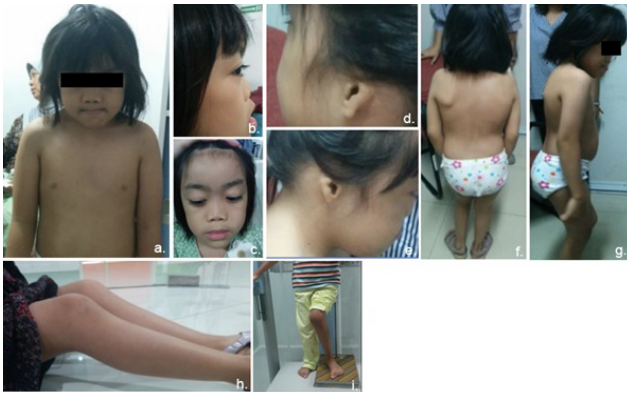

Figure 1: Patients physical examination **a.** Patients front view, **b.** Mid face hypoplasia, **c.** Hypoplastic nose, **d.** Microtia, **e.** Short neck, **f.** Scoliosis, **g.** Kyphosis, **h.** Contracture, **i.** Leg length discrepancy.

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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-surgery, a plaster cast was used to stabilize the left knee. One month 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

Figure 2: Patients giant before surgery.

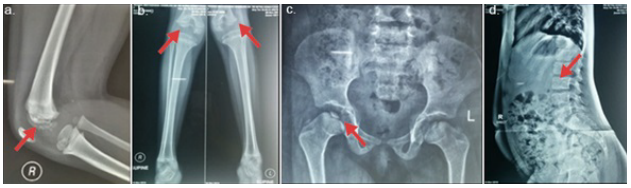

Figure 3: Patients bone survey, a. Metaphyseal dysplasia of the genu, b. Dysplastic distal femoral epiphyses with central metaphyseal clefts, c. Dysplastic femoral heads, d. Dense lines suggestive of previous coronal clefts of the vertebral body.

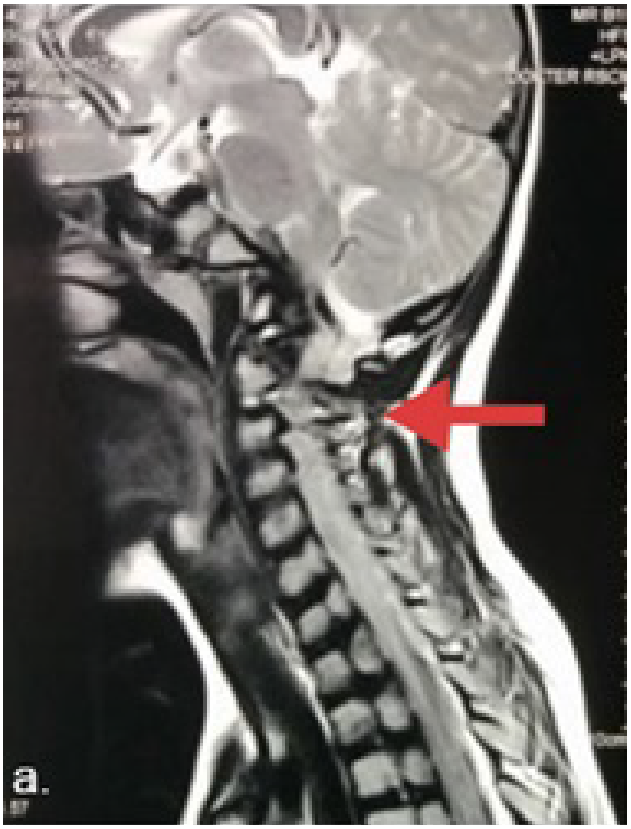

Figure 4: Patients cerebral MRI shows coronal vertebral clefts at cervicothoracal level and atlanto-axial dysplasia.

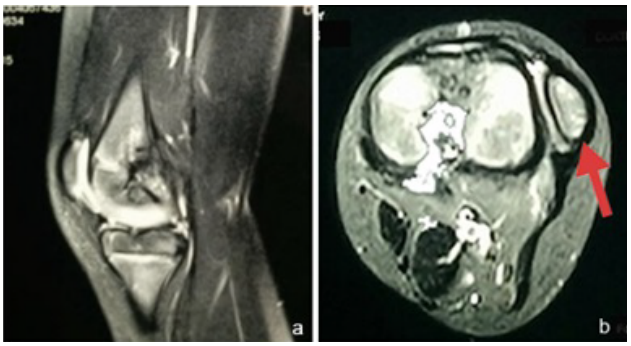

Figure 5: Patients knee MRI, a. Epimetaphyseal dysplasia of the distal femur, medial meniscus dysplasia and lateral meniscus tear, suspected anterior ligamentum cruciatum tear, b. Lateral dislocation of the patella.

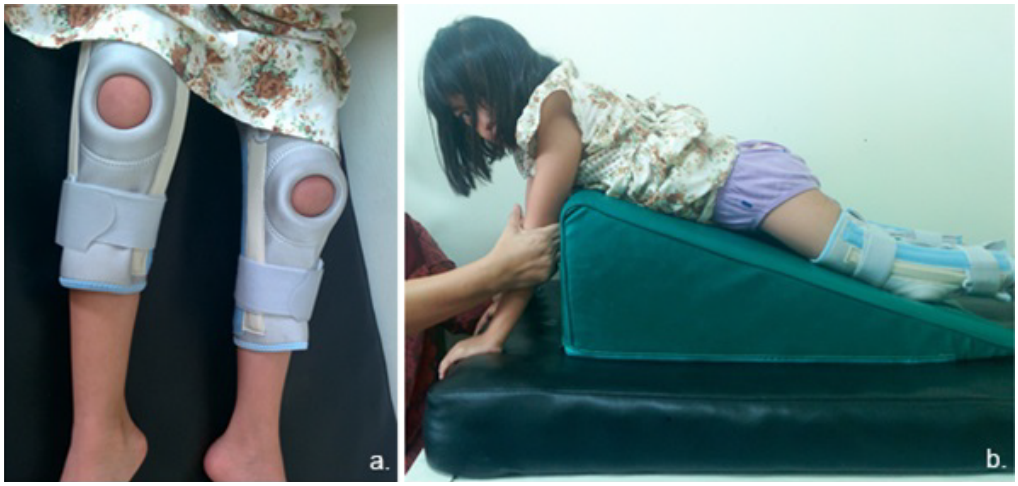

Figure 6: Post-operative. a. Bilateral knee brace, b. Rehabilitative procedures to release tightness on hamstring.

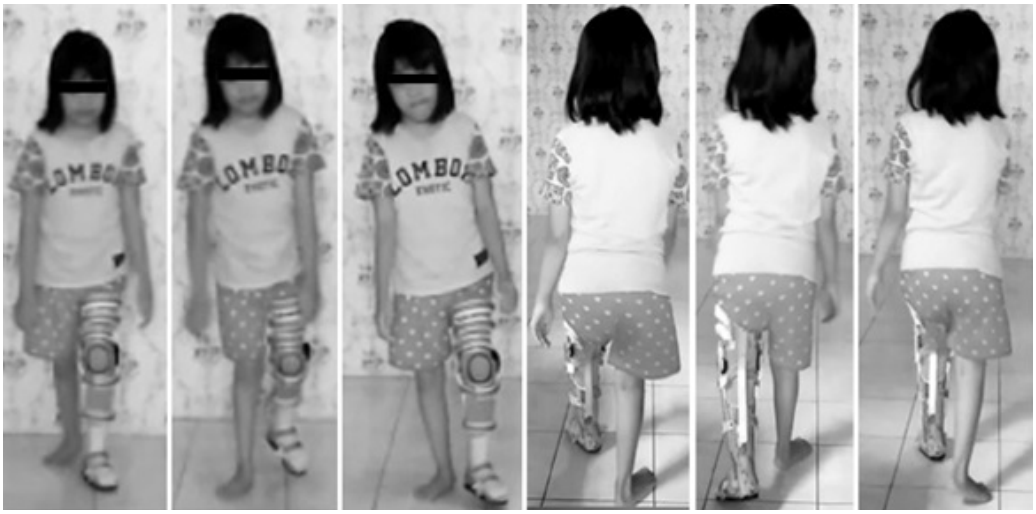

Figure 7: Patients gait 3 months post corrective surgery.

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 old1 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.

In addition, intraoperatively, it was concluded that the meniscus 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

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 3.3 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 elbo. Microepiphyses of femoral heads, metaphyseal widening, short femoral neck. Irregular metaphyses of the knees.	Dysplastic femoral heads at birth and showing bifid distal femur and markedly 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	Epimetaphyseal dysplasia of the distal femur, laterally dislocated left patella, posterior subluxation of the tibia, dysplasia of the medial meniscus, a tear in the lateral meniscus and the anterior cruciate ligament.
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 atalanto-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 hypoacusis	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 cutis on the skull vertex	Area of aplasia cutis on skull vertex	Two lateral hair whorls. No areas of aplasia cutis
Heart	Normal echocardiography	Normal echocardiography	ASD (spontaneously closed at age 20 months)	ASD (ostium secundum)	Patent foramen ovale and aneurysmatic septum	Normal echocardiography
Gastrointestinal	No data	No data	Anal atresia	Normal abdominal ultrasonography	Anal atresia	Normal abdominal ultrasonography
Kidney/urogenital	Normal ultrasound	Normal ultrasound	No abnormalities on ultrasound	1 UTI at 1 year but normal renal ultrasonography	Vesicoureteral reflux	Hypoplastic bilateral kidneys with normal kidney functions
Brain	No data	No data	Normal MRI at age 5 months	Normal cerebral ultrasonography	Agenesis 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.

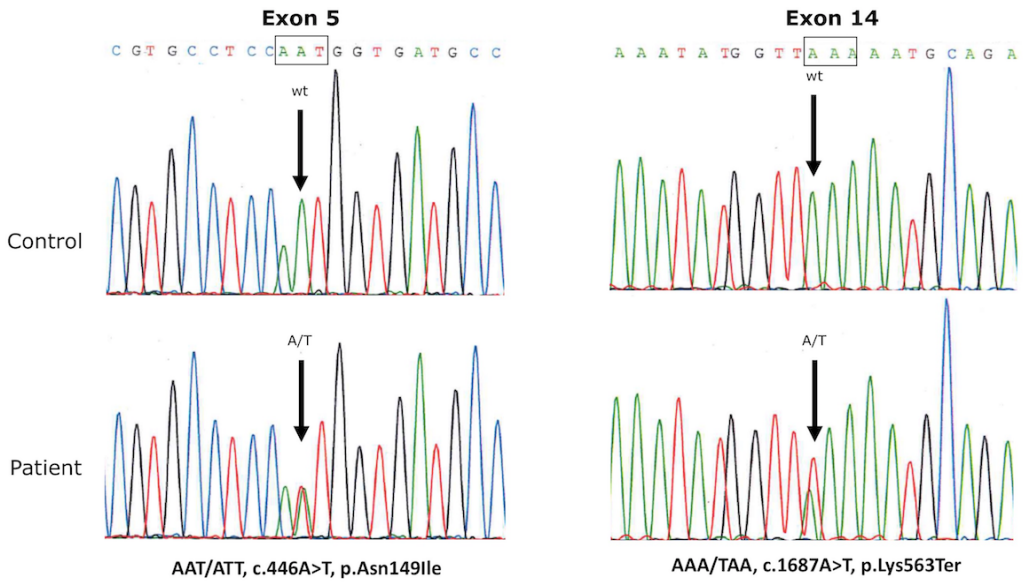

Figure 8: Result of gene sequencing.

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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