

Clinical Spectrum of Hereditary Spastic Paraplegia in Children

A study of 74 cases

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الطيف السريري للشلل السفلي التشنجي الوراثي في الأطفال

دراسة 74 حالة

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الملخص: الهدف: كان الهدف من هذه الدراسة هو استكشاف الشلل السفلي التشنجي الوراثي في الأطفال في سلطنة عمان. الطريقة: أجريت هذه الدراسة بأثر رجعي من الفترة ما بين يناير 1994 و أغسطس 2011 على الأطفال الذين يعانون من تأخر التطور النمائي، واضطرابات المشية، ومعوقات الحركة مع وجود علامات متناظرة السبيل الهرمي. تم تسجيل تاريخ الولادة والأسرة مفضلاً، بما في ذلك سن ظهور الأعراض. وصفت إصابات الأطفال بأنها إما نقية أو معقدة من طيف الشلل السفلي التشنجي الوراثي استناداً إلى معايير التشخيص المتبعة. في الأسر التي لديها طفل مصاب واحد أو أكثر، تم أيضاً فحص الآباء وجميع الأشقاء. النتائج: خلال الدراسة، تم تشخيص 74 طفلاً من 31 عائلة لديها الشلل السفلي التشنجي الوراثي. وجدت نسبة القرابة الأبوية في 91% من الحالات، 44 طفلاً (59.4%) يعانون من ظهور المرض في إطار عام واحد من العمر. كان معقد النوع الأكثر شيوعاً ووجد في 81.1%. وكان اكتناف الكلام والتخلف العقلي، والصرع والتشوهات المرتبطة الأكثر شيوعاً. لوحظت تغييرات غير محددة للمادة البيضاء وتشوهات الجسم القطني في 24.3% من الحالات في التصوير بالرنين المغناطيسي. الاستنتاج: وصفت الدراسة المظاهر السريرية في 74 طفلاً مع ظهور الشلل السفلي التشنجي متنحي الوراثة في 81.1%.

مفتاح الكلمات: شلل سفلي تشنجي؛ شلل سفلي تشنجي وراثي؛ وراثي متنحي؛ الأطفال ذوي الاحتياجات الخاصة؛ عمان.

ABSTRACT: Objectives: The aim of the study was to explore the spectrum of hereditary spastic paraplegia (HSP) in children in Oman. **Methods:** This retrospective study was carried out between January 1994 and August 2011 on children with delayed development, gait disorders and motor handicaps, with signs of symmetrical pyramidal tract involvement. A detailed perinatal and family history, including the age of onset of symptoms, was recorded. The children were labelled as having either the pure or complicated form of HSP based on the established diagnostic criteria. In families with more than one affected child, parents and all other siblings were also examined. **Results:** Within the study, 74 children from 31 families were diagnosed with HSP. Parental consanguinity was seen in 91% of cases, with 44 children (59.4%) experiencing onset of the disease under one year of age. Complicated HSP was the most common type, seen in 81.1%. Speech involvement, mental retardation, and epilepsy were the most common associated abnormalities. Nonspecific white matter changes and *corpus callosum* abnormalities were noted in 24.3% of cases on magnetic resonance imaging. **Conclusion:** The study described clinical features of 74 children with HSP. Autosomal recessive complicated HSP was seen in 81.1% of cases.

Keywords: Spastic Paraplegia, Hereditary; Spastic paraplegia, autosomal recessive; Disabled Children; Oman.

ADVANCES IN KNOWLEDGE

- This study examined the largest series of hereditary spastic paraplegia (HSP) in children in Oman.
- An autosomal recessive pattern of inheritance was seen in all cases in the study.
- Early onset of symptoms was seen in the majority of patients (~60%).
- Microcephaly was often seen in the children in this study.
- Magnetic resonance imaging showed white matter abnormalities in 24.3% of cases.
- A differential diagnosis of HSP should be considered if the history and clinical features do not suggest cerebral palsy.

APPLICATION TO PATIENT CARE

- Early diagnosis is essential in cases of HSP in children.
- Multidisciplinary care should be implemented as soon as the initial diagnosis is made in order to prevent handicaps.
- Support groups should be set up in Oman for children afflicted with HSP.

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- Genetic diagnosis should be undertaken for the families, and an antenatal diagnosis made, in order to prevent further cases of HSP in future pregnancies.
- Genetic counselling should be made available to affected families.

HEREDITARY SPASTIC PARAPLEGIA (HSP) is defined as a neurological disorder characterised by progressive symmetrical pyramidal tract dysfunction with onset in the lower limbs resulting in weakness, mainly of the lower extremities.¹ The onset of the disease can be from early childhood up to 70 years of age.² Childhood-onset HSP needs to be differentiated from more common conditions like cerebral palsy and other mimicking neurodegenerative disorders that particularly affect the white matter of the brain.³

HSP is classified as either pure or complicated based on well-established criteria.^{4,5} The disease is mainly reported in adults and there have been only a few studies in children.^{5,6} Autosomal dominant, X-linked and autosomal recessive modes of inheritance have been described.⁷ The autosomal dominant variety is the most common type, reported in 70–80% of all cases of HSP seen so far.^{5,8} Previous data from Oman were limited to two reports of two large families involving 16 children with novel genetic mutations.^{9,10} The present study describes clinical features of HSP in 74 children, including the previous study of 16 children in which a genetic work-up has already been done.

Methods

This work was carried out from January 1994 to August 2011 at the Sultan Qaboos University Hospital (SQUH), Muscat, Oman, which is one of Oman's tertiary referral hospitals. Children with delayed development, gait disorders and motor handicaps, who had signs of symmetrical pyramidal tract involvement, were included. Children who had been diagnosed with cerebral palsy at another hospital or had been referred for neurological opinion were also included if the features were suggestive of HSP.

A detailed history was taken for all cases regarding perinatal events, the age of onset of symptoms and the family history. All children were examined independently by two child neurologists and their HSP was classified as pure or complicated based on the established diagnostic criteria.^{4,5} In

families with more than one affected child, the parents and all other siblings were examined for abnormal neurological signs. Affected cousins could not be examined as they refused to come for a check-up.

An intelligence quotient (IQ) assessment was done only in one child as the majority of the children in the study (60%) were under one year of age. Cognitive impairment (mental retardation) was assessed based on the achievement of mental and social milestones and on a developmental assessment test administered at the time of clinical examination. Ophthalmological check-ups were performed in all cases. Besides baseline blood tests and tandem mass spectrometry, an assessment of lactate, ammonia and creatine kinase levels was also performed for all cases. When indicated, lysosomal enzymes, very long chain fatty acids, plasma amino acids, and urine organic acids were also estimated. Oman's population has a large number of metabolic and neurodegenerative disorders; however, these were excluded on clinical features and appropriate laboratory investigations. Vitamin B12 levels were also tested if a deficiency was suspected. Magnetic resonance imaging (MRI) scans of the brain and spinal cord were done in all cases at the time of presentation and in 12 others on follow-up.

The progression of the disease was based on the clinical criteria of worsening spasticity and gait, deterioration of muscle power and declining school performance. Nerve conduction studies, brainstem auditory evoked potentials (BAEPs) and visual evoked potentials (VEPs) were performed in all cases. An electroencephalograph was recorded if there had been a history of seizures. A genetic work-up was done in the two large families who had been studied and reported earlier.^{9,10} A second study, to define the underlying genetic changes for the rest of the children, is planned in the near future.

The basis for the diagnosis of pure HSP was drawn from already-established criteria.^{1,4,5} First, children were considered developmentally delayed based on slow development or walking gait abnormalities with a static or slowly progressive course, and examination findings of symmetrical

Table 1: Various clinical features in children with hereditary spastic paraplegia

Feature	n	%
Age of onset		
Birth	15	20.27
Less than 6 months	12	16.21
6 months–1 year	17	22.97
1–4 years	12	16.21
4–10 years	15	20.27
10 years and above	3	4.05
Speech abnormalities		
Dysarthria	16	21.60
Language delay	6	8.10
Developmental aphasia	5	6.75
Normal	47	63.50
Mental retardation	17	22.97
Epilepsy	13	17.56
Cerebellar features	9	12.16
Microcephaly	8	10.80
Extra pyramidal features	6	8.10
Simple febrile fit	1	1.35
Eye changes		
Pigmentary retinopathy	4	5.40
Anterior dystrophy	1	1.35
Optic disc pallor	1	1.35
Abnormal MRI findings		
Nonspecific white matter changes	12	16.21
Corpus callosum thin/agenesis	10	13.50
Cerebellar volume reduction	1	1.35
Neurophysiology		
Nerve conduction abnormal	1	1.35
BAEP abnormal (delayed/flat)	5/3	6.75/4.05
VEP poor waveform	1	1.35

MRI = magnetic resonance imaging; BAEP = brainstem auditory evoked potential; VEP = visual evoked potential.

pyramidal tract features (weakness, hypertonia, hyperreflexia, upgoing plantars, plantar flexion of the feet and contractures at a later stage) mainly affecting lower limbs, with normal or minimal involvement of the upper limbs. Second, a family history of a sibling or a cousin with a similar illness was an important indicator of the condition. Third, MRIs of the brain and spinal cord that were normal

or had nonspecific white matter changes (white matter hyperintensities) in the brain at the time of initial presentation or on follow-up were also included if clinical features were suggestive of HSP.

The basis for the diagnosis of complicated HSP was the presence of one or more features such as microcephaly, seizures, mental retardation, delayed language development, dysarthria, abnormal eye findings, progressive course and abnormal imaging, in addition to the features of pure HSP.

Exclusion criteria included: 1) children with static encephalopathies (cerebral palsy) related to perinatal complications; 2) those with diseases affecting the grey/white matter of the brain (gangliosidoses, leukodystrophies) and 3) the presence of basal ganglia disorders, hereditary neuropathies, vitamin B12 deficiencies, spinal cord trauma or demyelinating diseases.

This study was approved by the ethical committee of the College of Medicine & Health Sciences at Sultan Qaboos University.

Results

In the course of our study, 74 children with HSP were seen (42 males [56.8%] and 32 [43.2%] females). At the time of initial diagnosis, 42 were labelled as complicated HSP; 18 others progressed on follow-up and 14 were determined to have the pure form of HSP. The age of onset was under one year in 44 (59.4%) children. The children diagnosed in the initial years are adults now and have experienced progression of the disease. In 30 families, there was more than one child affected. Only one family had a single case, which was presumed to be sporadic. On having more children, the chance of having another child affected with the disease is possible. The age of initial presentation ranged from 7 months to 15 years, 5 months, with a mean of 5 years, 8 months. All children had normal perinatal histories. Parental consanguinity was seen in 91% of the children. There was an additional family history of affected cousins in 6 of the families. However, the cousins were not examined as they were reluctant to visit the hospital; hence, they were not included in the study. Cognitive impairment (mental retardation) was seen in 17 children (23%). Speech-related problems, mainly delayed language and dysarthria, were seen in 27 (36.5%). Ophthalmologic examinations showed retinal pigmentary changes in four cases,

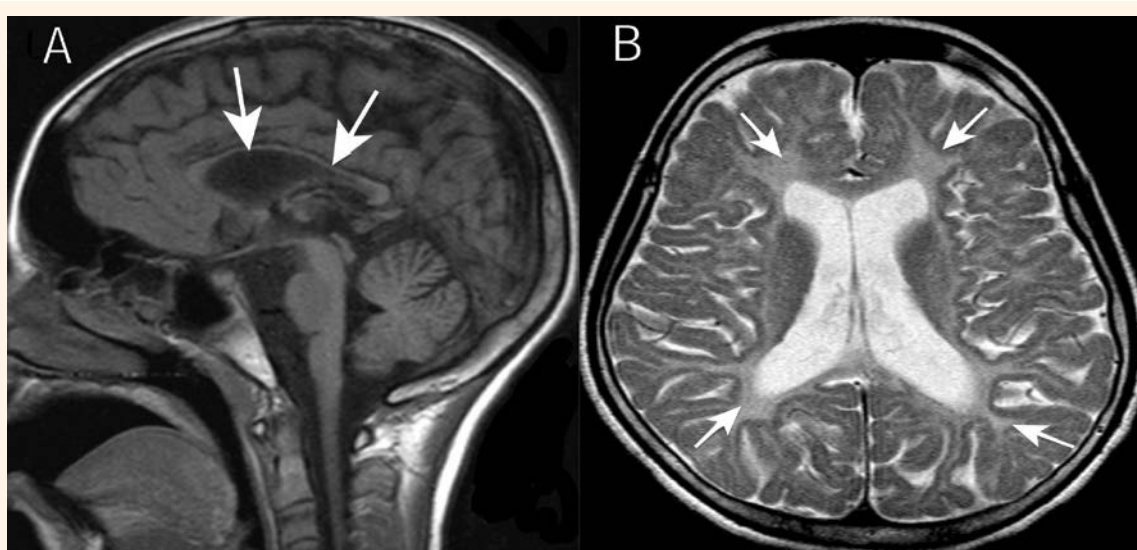


Figure 1 A&B: Magnetic resonance imaging scan of the brain of a 13-year-old girl. (A) Sagittal T1W view showing moderate hypoplasia of the *corpus callosum* (arrows). (B) Axial T2W view showing non-specific hyperintense signal abnormalities in the periventricular white matter (arrows).

anterior dystrophy in one, and optic disc pallor in one. The details of other features are given in Table 1.

Neurometabolic disorders were initially suspected in a few children, but the disorders were excluded by performing tandem mass spectrometry, or by estimating lysosomal enzymes, very long chain fatty acids or urine organic acids. The vitamin B12 levels assessed in 6 children were normal. One child with HSP, who was suspected of having myopathy, underwent a muscle biopsy outside the country; the results were normal. Brain abnormalities, detected upon MRI, were noted in 18 cases. These abnormalities were noted at the first presentation or later on follow-up. MRI changes that were not noted initially in 12 children eventually appeared in 3 on follow-up examinations performed after the children's symptoms worsened clinically. Overall, twelve children had nonspecific white matter changes (white matter hyperintensities) [Figures 1B and 2B]. A total of 10 children had *corpus callosum* changes ranging from thin to absent, in addition to white matter changes [Figures 1A and 2A]. Basal ganglia and spinal cord abnormalities were not seen in any children. Entire brain volume reduction was noted in one child and another had cerebellar atrophy. Nerve conduction studies were normal in all except one. This patient had features of hereditary demyelinating motor sensory neuropathy. Brainstem AEPs were delayed in 5 children, while two had no response. VEPs were

normal in all except one, who had poor waveform.

There are approximately 45,000 live births per year in Oman. As 74 children were seen over 18 years, this gave an approximate incidence of 1 in 11,000 live births. The incidence could be higher than this as patients of other tertiary care hospitals were not included in this study.

All the children in this study were managed by supportive therapy, including muscle relaxants, physiotherapy and occupational therapy. Some children received botox and a few had corrective orthopaedic surgery. One child underwent selective dorsal rhizotomy in the USA.

Discussion

Reaching a diagnosis of HSP is relatively challenging in the first two years of a child's life when all investigations are normal and there is no relevant perinatal history indicating brain insult suggestive of cerebral palsy. A slowly progressing gait disorder with dominant pyramidal signs in the lower limbs and none or few sensory symptoms favour a diagnosis of HSP.^{1,2,7} Various other neurodegenerative disorders affecting the neuroaxis at this age need to be differentiated if the typical clinical features of a particular disease are not present.⁶ A detailed algorithm for the diagnosis of HSP in children must be followed.⁶ The differential diagnosis in paediatric-onset HSP is different from the adult-onset type, as many

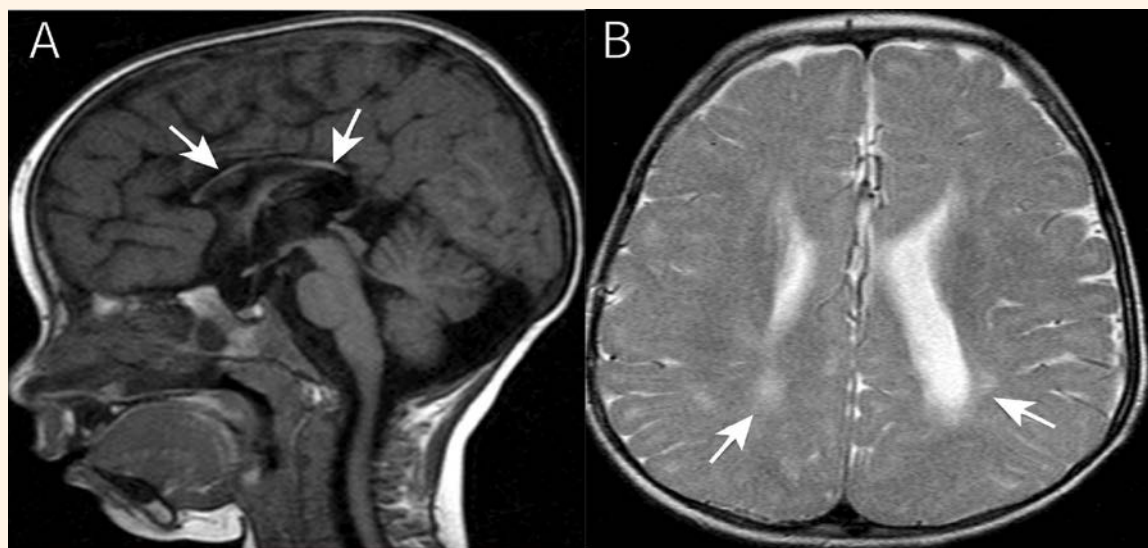


Figure 2 A&B: Magnetic resonance imaging scan of the brain of a four-year-old boy. (A) Sagittal T1W view demonstrating marked hypoplasia of the *corpus callosum* (arrows). (B) Axial T2W view showing hyperintense signal abnormalities in the periventricular trigon white matter (arrows).

children are misdiagnosed with cerebral palsy.^{6,7} HSP should be considered a diagnosis of exclusion in children.⁵ Important diagnostic alerts against it are bulbar signs, early amyotrophy, asymmetric pyramidal tract lesions, extra pyramidal signs and peripheral neuropathy.⁵

The presence of more than one affected child in a family or affected cousins was very helpful in making the HSP diagnosis. Following strict diagnostic criteria, we were able to give a detailed description of HSP in the children in our study, most of whom are still being followed-up at SQUH to look for progression of the disease and manifestations of any other disorders developing over time. As Oman has a large number of metabolic and neurodegenerative disorders, doctors must watch for the presence or development of other neurological disorders; however, none of our children have yet developed features of other neurological disorders.

HSP is mainly reported in adults; there have been only a few studies in children.^{5,6} The autosomal dominant variety is the most common type reported, constituting 70–80% of all cases.^{5,8} We did not encounter cases with an autosomal dominant or X-linked inheritance pattern. An examination of siblings and parents was important for excluding this pattern of inheritance. All children in this study had an autosomal recessive inheritance pattern. Consanguinity may be the main underlying factor as consanguineous marriages are common in Oman. Depending upon the disease entity, consanguinity

has been reported in 56.3–87.50% of cases.^{11,12}

Two forms of HSP were described initially: pure and complicated.² Mainly pyramidal features and mild sensory abnormalities were noted in the pure form. Other neurological and non-neurological features were seen in the complicated form. Recently, diagnostic criteria for pure and complicated HSP have been suggested.⁵ The differentiation between the pure and complicated forms was evident upon presentation in 42 cases, while 18 were seen to progress over time. By their second decade, many of the children in this study had developed speech impairments, dysarthria, a decline of intellect, cerebellar disorders and a loss of ambulatory function. These features suggested the complicated form of HSP. The majority (81.1%) of the children in our study had complicated HSP which also comprised 65% of cases in an earlier study.¹³ In another series of 72 children, autosomal recessive HSP was seen in 17%, and 25% of these cases had complicated HSP.⁶ This wide variability in the pure and complicated forms in our study may be related to the particular cohort of patients, the geographical location, patient genetics and the possibility of consanguinity in the population. Other than these factors, the accuracy of a diagnosis of pure HSP has been questioned in the past.¹⁴ Observations of the children in this study lend further evidence to the hypothesis that the pure form of HSP is rare in children, in contrast to adult-onset autosomal dominant HSP. Over time, most patients invariably

fall into the group of complicated HSP.

A large number of the children in this study (59.45%) presented with symptoms at under one year of age, and the majority (56/74, 75.67%) presented at under 4 years. It was found that 20% had onset from birth, and 16% at around 6 months of age. This observation was based on the history taken from the parents. It was observed that the children with onset at under one year continued to achieve milestones, although with delays, up to the age of about 4 years and that subsequently progressive weakness started. This could be related to a growth spurt overtaking the disease process in this age group, as observed in many neurodegenerative diseases. This was not noted in the children with onset after 4 years of age. These children continued a downhill course after the onset of weakness.

Speech involvement was noted in 27 children (36.5%), dysarthria being the most common (16, 21.6%), while 6 (8.1%) had delayed language development. Mental retardation was noted in 17 (23%) cases of complicated HSP in the current study. Cognitive impairment over time has been reported in all types of HSP.⁵ Mental retardation in HSP has been reported in several previous studies.^{5,7,15–19} Some of our patients experienced a worsening of cognitive functions with disease progression, as noted previously.^{19,20} However, in this cohort, this observation could not be substantiated by an appropriate IQ assessment.

Epilepsy is not a common feature of HSP; however, there are case reports and families with special genetic abnormalities associated with epilepsy.²¹ Epilepsy was noted in 13 (17.5%) of our patients; 3 of them had a thin *corpus callosum*.^{9,10} Different types of seizures have been associated with HSP.^{5,21} In the current study, tonic-clonic seizures were found in 7 children, myoclonic in 4, and partial in two. Cerebellar features may be seen at the onset of the disease or later on after progression of the disease.^{5,9,10,17,20,22} In severe cases with spasticity and contractures, cerebellar features may be difficult to recognise. Cerebellar features were seen in 9 children (12.1%), although MRI scanning showed cerebellar atrophy in only one.

Microcephaly is an uncommon feature in adult-onset cases of HSP and has been reported only in a few studies.^{5,15,23} It was noted in 8 (10.8%) of our patients; this is suggestive of early onset illness affecting brain growth and development. Those

with adult-onset HSP initially had normal brain growth and development—hence the normal head size. Extrapyramidal features, mainly in the form of dystonia, were noted in 6 (8.1%) of our patients although no imaging changes in the basal ganglia were seen, except generalised atrophy (decreased brain volume) in one child. This may be a part of the global atrophy of the brain noted in some of these patients.⁵

Eye abnormalities in the form of pigmentary retinopathy and disc pallor were noted in 6 (8.1%) patients. Eye abnormalities like macular changes, pigment migration, and atrophy have been reported previously in other studies.^{5,17,24,25}

The majority of children with HSP have normal MRI results, as was seen in 75.6% of our patients. Abnormal MRI images were seen in 18 (24.3%) patients in the white matter, *corpus callosum* or both. Nonspecific white matter changes in the brain, namely leukoencephalopathy or white matter hyperintensities, were the most common findings in these children, and were noted in 12 out of 18 (66.7%). These white matter changes have been reported before in the literature.^{9,10,17,20} Loss of volume (thinning) and agenesis of the *corpus callosum* were seen in 10 out of 18 (55.5%) patients. Involvement of the *corpus callosum* was the second most common abnormality found by MRI in our patients. There are several reports in the literature of white matter hyperintensities (diffuse or patchy) and *corpus callosum* abnormalities in association with HSP.^{9,10,17,19,20,26–30}

Thinning of the cervical and thoracic spinal cord has been noted in HSP.³¹ Volume loss is an expected finding as there is a degeneration of the longer corticospinal tracts to the spinal cord (mainly to the lower limbs) and dorsal column pathway within the spinal cord.^{5,32} However, this has not been noted in our patients to date. This study noted abnormalities at initial presentation or on follow-up in the brain MRIs only, but no changes were seen on follow-up in the spinal cord in the few children who underwent repeat MRIs. It may be possible to see these changes in the spinal cord at a later stage.

In most cases of pure HSP, nerve conduction studies are normal.² Sensory impairment has been reported in 10–65% of cases of pure HSP; however, nerve conduction studies have been found to be normal.^{5,17,25,33} Sensory abnormalities on clinical examination in children are the most difficult ones

to detect. In this study, all children had normal nerve conduction velocities except in one whose abnormality was associated with hereditary motor sensory neuropathy. Abnormalities of the central motor conduction times have also been reported. Abnormalities of somatosensory evoked potentials in the form of low amplitudes also have been reported.³⁴ Similarly, abnormal BAEPs and VEPs have been reported previously. These are rare manifestations in HSP.^{34–36} We found abnormal BAEPs in 5 patients (6.7%) and VEPs in one (1.3%).

The most common genes associated with recessive HSP are *SPG5A*, *SPG7*, *SPG11*, and *SPG15*.² The pure form with variable age of onset and slow progression is located in the *SPG5A* gene.²² In the two previous studies from Oman on 16 children, 9 children with complicated HSP were genetically mapped to a new locus on 8p12-p11.²¹ and 7 children with the *SPG35* gene were mapped to 16q21-q23.^{1,9,10} In the rest of the children, genetic studies are expected to be undertaken in the future. Specific molecular genetic tests will help in easy and early diagnosis and help patients to avoid invasive and costly work-ups.² In over 50% of cases of autosomal dominant HSP, a molecular diagnosis is possible.² The *loci* of at least 44 spastic paraplegia genes have been mapped, and 20 genes have been identified to date.^{2,20} A systematic review of clinical features and genetic studies from 1985 to 2008 was reported in a recent study.²

There are several hypotheses to explain the pathophysiologic mechanism of HSP. Malfunction of the axonal transport and membrane trafficking are emerging as likely mechanisms.^{2,37} Interference in the axonal transport of macromolecules, organelles and their cargoes to the longest neurons in the spinal cord result in HSP.^{37,38} Mitochondrial dysfunction could also affect the efficient transport of signals, molecules, and organelles to and from the nerve terminals.²⁰ Mutation of fatty acid 2-hydroxylase (FA2H) was reported as the underlying mechanism of the complicated form of HSP in *SPG35*.²⁰

Management of these HSP-affected children is a challenge. Multidisciplinary approaches involving several specialties can help them and their families. Locating the responsible genes and understanding the disease mechanism, and then translating these findings into therapies is a long term undertaking.^{38,39} The goal for the future is to prevent such severe forms of autosomal recessive HSP. Genetic studies

will help in the accurate diagnosis of patients, the detection of asymptomatic cases and prenatal diagnosis in families. This will eventually prevent the disease.

Life expectancy in those with adult-onset HSP is mostly normal.^{5,7} This may not be true in children as we have seen children become wheelchair-bound by their teens. The oldest survivor in this study is a 23-year-old male who is bedridden and severely handicapped.

This study had the limitation that there was no supportive genetic study on 58 of the patients. It is possible that some rare neurometabolic disorder may be detected in some of them on long-term follow-up.

Conclusion

Autosomal recessive complicated HSP is the main form of HSP seen in children in the Arabian Peninsula, with an approximate incidence of 1 in 11,000 live births. The majority of children experience onset at under 4 years of age. In the initial few years, they do not show deterioration in motor functions but then show progressive weakness. Speech involvement, mental retardation, epilepsy and microcephaly were commonly associated features in this study. Future genetic studies should reveal whether these children are experiencing a different genetic mutation from the previously identified genes involved in HSP or have totally novel mutations.

DECLARATION

The authors declare no conflict of interest in this study, and that no financial help was received for the study from SQUH or any private party.

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