A novel autosomal recessive “Huntington’s disease-like” neurodegenerative disorder in a Saudi family

Abdelrahman Y. Al-Tahan, MD, FRCP, Madai P. Divakaran, MD, MRCP, Marios Kambouris, PhD, FACMG, Saeed Bohlega, MD, FRCP, Mustafa Salih, PhD, MRCP, Adesola Oginni, FWACP, Hussein Al-Ghanmi, MRCP.

ABSTRACT

Objectives: To study a Saudi family affected by an unusual neurological disorder, in order to clarify its different clinical, investigational and genetic aspects.

Methods: Patients were identified through a preliminary clinical examination of all family members and their relatives. Then they underwent a meticulous clinical assessment and detailed general and metabolic investigations, neurophysiological and radiological tests, and genetic analysis.

Results: Five siblings suffered from an autosomal recessive disorder simulating clinically and radiologically the rare juvenile Huntington’s disease. The disease manifests at an early age with mental deterioration, speech disturbance, dystonia and other extrapyramidal and pyramidal features. Although results of genetic studies excluded Huntington’s disease, they also indicate that the Huntington gene is a genetic marker for this disease.

Conclusion: This family suffers from a novel neurodegenerative inherited disease, the gene of whom is probably localized on chromosome 4.

Keywords: Dementia, extrapyramidal, Huntington’s disease, autosomal recessive, early onset.


In the past few decades medical services have spread throughout the Kingdom of Saudi Arabia, with the emergence of many recently acquired highly developed genetic studies units. Apart from improving health care standards, this has led to the identification of many new or rare inherited diseases. This reflects some degree the rather special situation in this country promoted over hundreds of years by the effect of a high consanguinity rate in tribal and close communities.

In this paper, we describe a Saudi family from Najran, an ancient city at the far southwest of the Kingdom, affected by an unusual inherited disease manifested at an early age with progressive speech difficulty, mental deterioration and movement disorder.

Methods. All members of the proband’s family and their relatives, who suffer from any neurological disorder underwent an outpatient clinical assessment. One male relative diagnosed as cerebral palsy, and another deaf-mute boy as congenital sensorineural deafness. Patients were admitted to hospital for detailed clinical assessment and full relevant metabolic, neurophysiological and radiological investigations. A simultaneous genetic study started in collaboration with the genetics laboratory at King Faisal Specialist Hospital.

From the Departments of Medicine (Al-Tahan, Oginni, Al-Ghanmi) and Pediatrics (Salih), King Khalid University Hospital, Department of Medicine, King Khalid Hospital, Najran (Divakaran) and the Department of Neurosciences (Bohlega) and Genetics Unit (Kambouris), King Faisal Specialist Hospital and Research Center, Riyadh, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Abdelrahman Y. Al-Tahan, Associate Professor of Neurology, King Khalid University Hospital/ King Saud University, PO Box 7805 (38), Riyadh 11472, Kingdom of Saudi Arabia. Tel. No. 966-1-467 1532. Fax. No. 966-1-467 2424.
Results. Five siblings, 3 sisters and 2 brothers, from a total of 10 were affected. Parents were healthy first-degree cousins, implying that the mode of inheritance is most likely autosomal recessive (Figure 1). Data on each of the 5 patients is described below.

Patient 1. The proband is an 18 year old man, with normal early milestones including motor and language development. At the age of 5 years, his speech became progressively incoherent, hand movements became clumsy and his gait unsteady. Soon he started to have involuntary movements involving the limbs and trunk and causing deforming postures. His illness restricted his ability to receive any formal education. By the age of 12 years, he became mute; wheelchair bound and started to have attacks of tonic movements of the upper limbs with rolling up of both eyes. These were labeled as epileptic seizures and were unsuccessfully treated with multiple anticonvulsants. Soon afterwards, he became fully dependent and was admitted into a chronic care institution. His medications included Telegotol and Haloperidol.

On examination (Figure 2), he looked severely emaciated with widespread contractures and flexion deformities, associated with multiple bedsores. He was alert but mute, responding to verbal stimuli with localizing full eye movements. Muscle tone was increased with brisk deep tendon reflexes, but plantar responses were flexor. There were minimal limb voluntary movements. Coordination could not be tested and sensation was grossly intact.

Investigations included normal cell blood count (CBC), renal and liver function tests; as well as serum amino acids profile, serum and urine uric acid and urine amino and organic acids. Copper metabolism studies as well as slit-lamp examination were within normal limits. Electroencephalogram (EEG) showed excessive bilateral fast activity with normal background and absence of epileptogenic activity. Nerve conduction studies (NCS), visual evoked potentials (VEP), electroretinogram (ERG) and brainstem auditory evoked responses (BAER) were normal. Brain computerized tomography (CT) scan and magnetic resonance imaging (MRI) revealed similar changes of mild generalized cortical atrophy mainly affecting the frontal lobes and bilateral caudate nucleus atrophy (Figure 7), whereas single photon emission tomography was normal.

Patients 2 and 3 (Figures 3 & 4). Included the eldest affected sibling, a 20 year old sister and a 17 year old brother. Both had history and physical findings similar to Patient 1.

Patient 4 (Figure 5). A 13 year old girl who presented, since the age of 4-5 years, with similar symptomatology and did not attend any formal schooling. She was almost fully dependent, could not feed herself, was doubly incontinent but had normal sleeping pattern. At the age of 7 years she started to have frequent episodes of flexion and crossing of both upper limbs and extension of lower limbs, but she never lost her consciousness. She was mentally retarded, responding inconsistently to simple commands with incoherent speech. She was anxious and had episodes of excessive crying or laughter. On this account, she was treated with Haloperidol in combination with anticonvulsants. She displayed frequent choreo-atheletic movements with variable limb and trunk abnormal posturing. Muscle tone was increased with exaggerated deep tendon reflexes and equivocal plantar responses. She was able to walk unsteadily with assistance.

Patient 5 (Figure 6). Eleven year old girl who was noted to have progressive deterioration of speech and mobility as early as 3-4 years. She became totally mute at 6 years of age, walked only with help, needed partial assistance for feeding and was doubly incontinent. She had abnormal choreiform movements and was treated with Haloperidol. When examined she was found to be mute, calm and responding poorly to simple commands. She could move all limbs voluntarily, had poor facial expression and full extraocular eye movements. She had generalized rigidity and exaggerated deep tendon reflexes. No definite evidence of cerebellar dysfunction could be elicited.

Investigations in patients 2 to 5 showed normal CBC, blood film, renal and liver functions, serum and 24-hour urine copper, serum ceruloplasmin and slit-lamp examinations, as well as amino acid profile and uric acid. Urine analysis for uric acid, aminoacids and organic acids were carried out for patients 4 and 5 and were within normal limits. NCS, VEP, ERG, BAER, and multiple video-EEG recordings were within normal limits in these 2 patients together with normal brain MRI and positron emission tomography.

Molecular DNA testing for the Huntington triple nucleotide CAG repeat showed that 4 affected (Patients 1, 2, 3 & 4) and one normal sibling were homozygous for 18 CAG repeats while the last
Figure 2 - Patient number 1, the proband. He is inanimate, severely rigid, and mute but alert with full extraocular eye movements.

Figure 3 - Patient number 2. Note the severe dystonic features in both feet.

Figure 4 - Patient number 3.

Figure 5 - Patient number 4. Note the awkward gait and abnormal posture of the left foot.

Figure 6 - Patient number 5. Note her need for assistance in walking.

Figure 7 - MRI of patient number 1, showing moderate bifrontal and caudate nuclei atrophy.
The above described clinical picture suggests a novel inherited disease in the family. The clinical features, including delayed motor development, intellectual impairment, and abnormal eye movements, are consistent with the phenotype described in patients with bilateralbasal ganglia involvement. These features are not usually seen in typical Rett syndrome, suggesting the presence of a novel disorder. The clinical manifestations are similar to those reported in the classical Rett syndrome, but the age of onset and the clinical course are distinct. The clinical features are compatible with a disorder similar to Rett syndrome, but with a different pattern of symptom expression.

Table 1 - Differential diagnosis of reported family

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Intellectual disability</td>
<td>Rett syndrome</td>
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<tr>
<td>Motor development delay</td>
<td>Rett syndrome</td>
</tr>
<tr>
<td>Abnormal eye movements</td>
<td>Rett syndrome</td>
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<tr>
<td>Bilateral basal ganglia involvement</td>
<td>Rett syndrome</td>
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Discussion

Five members of this family are affected (patients 1 and 3), and 3 normal siblings were also affected. The patients' clinical features were consistent with Rett syndrome. However, the presence of bilateral basal ganglia involvement suggests a novel disorder. The clinical picture is similar to Rett syndrome, but with a different pattern of symptom expression. The diagnosis of Rett syndrome is confirmed by the typical clinical features, including delayed motor development, intellectual impairment, and abnormal eye movements. However, the presence of bilateral basal ganglia involvement suggests a novel disorder. The clinical features are compatible with Rett syndrome, but with a different pattern of symptom expression.
parkinsonism, and dystonia rather than chorea. Onset of HD as early as 4 years or less is well recognized, although the age of onset of juvenile variety is usually 10-15 years. Furthermore, neuroradiological changes in our patients (Patient 1 - Figure 7) are similar to those described in HD, but inheritance in our patients is clearly autosomal recessive, which has never been reported in HD. However, preliminary results of an ongoing genetic study excluded HD, and confirmed at the same time that Huntington’s gene is a marker for this disease.

References