First Cases of Uner Tan Syndrome in Anatolia, with Progressive Motor Improvement, Adaptive Self-Organization and Emergence of Late Childhood Quadrupedalism

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Abstract

**Background.** Uner Tan Syndrome (UTS) was first described in 2005 and consists of three main symptoms: habitual locomotion on all four extremities, impaired intelligence with no conscious experience, and dysarthria. Since then, seven further families have been found, mostly in southern and eastern Turkey, giving a total of 23 individuals in eight families exhibiting UTS. We here present three new cases with late onset UTS residing in central Anatolia.

**Methods.** The family’s five children were given thorough neurological examinations, and blood samples were taken for genetic analysis. Sagittal and coronal MRI scans were performed, and videos were recorded of their locomotion.

**Results.** The pedigree suggested an autosomal recessive inheritance. All of the affected children (3/5) were born with severe hypotonia, but by the time they were three they could sit and crawl on hands and knees, and at eight they could stand up and walk upright despite severe truncal ataxia. It was around this time that they started to walk on all four extremities, first with some difficulty, but then with a fully developed skill and ease in quadrupedal locomotion. As well as quadrupedal locomotion, the patients exhibited the other symptoms of UTS: little or no speech, and severely impaired intelligence.

**Conclusions.** These newly discovered cases suggest a late onset Uner Tan Syndrome, with habitual quadrupedal locomotion emerging when the patients were eight years old. It was suggested that an adaptive self-organization process lasting for about eight years caused the emergence of human quadrupedalism in these patients as a result of dynamic interactions of many elements within the main dynamic system.

Introduction

A novel syndrome with three main symptoms: habitual quadrupedal locomotion, mental retardation, and dysarthric speech — or no speech — was first described in 2005, in a consanguineous family residing in a small Turkish village near the Syrian border [1-3]. Subsequently, 23 cases were found in 13 families resident mostly in southern Turkey [4-11]. The patients with the syndrome, which came to be known as “Uner Tan Syndrome” (UTS), were usually found in families with consanguineous marriages.

A summary of the hitherto found and published cases of UTS is presented in Illustration 1. A review article of UTS was recently published [12]. Essentially, the individuals affected with UTS exhibited habitual quadrupedal locomotion instead of the upright bipedal locomotion normally acquired during childhood. They exhibited truncal ataxia, difficulties in stepping, mild to severe mental retardation with no conscious experience, dysarthric or no speech, with sounds ranging from a single sound to a few sounds. MRI scans of most patients showed cerebello-vermial hypoplasia and gyral simplification in the cerebral cortex, but one case had a normal brain MRI (see Families A to E in Illustration 1).

A few variants of UTS were also discovered. For example, there were two children with facultative quadrupedalism, who preferred quadrupedal locomotion for fast actions and bipedal locomotion for routine daily activities (Family E); one child developed late childhood quadrupedalism (Family F). There were two cases with a transition from quadrupedalism to bipedalism and one with consistent quadrupedalism (Family G). The families resided in southern and eastern regions of Turkey, and one in northern Turkey. A brief history of the discovery of UTS and discussion of human evolution in reverse was published elsewhere [13]. The present work will present further new cases exhibiting this extremely rare syndrome, referred to as “Uner Tan Syndrome,” which is the first report of UTS in central Anatolia.

Methods

The new UTS cases were members of a poor family
residing at the top of a hill in a small village near Afyon Karahisar, within the region of middle Anatolia. Of five siblings, one was severely disabled, being unable to stand up or walk at all, three exhibited all symptoms of UTS, and the fifth was normal. One of the authors (MT), who is a professor of neurology, performed the traditional neurological examinations (muscle tone and strength, gait, language, mental status, tendon reflexes in the upper and lower extremities, Babinsky sign, spasticity, nystagmus, strabismus, and cerebellar ataxia tests). The height, weight, and head circumference were within normal ranges for the Turkish population. Blood samples were taken from cubital veins and sent to the molecular biology department of the Bilkent University in Ankara for the genetic analyses.

The locomotion of the affected individuals was filmed using a video camera, for a subsequent analysis of their locomotor characteristics. Next day, we transferred the family members to the governmental hospital to perform sagittal and coronal MRI scans of all five siblings, using a 0.5 Tesla magnetic resonance scanner. The father provided written consent prior to the examinations on behalf of all the affected individuals. The study was approved by the ethical committee of the Medical School of Cukurova University.

Results

The parents had a consanguineous marriage, the father being the son of his wife’s uncle. They had five children: three daughters and two sons (see illustration 2), but there was only one healthy individual among the siblings (D3). According to the mother’s information, all three UTS cases showed postnatal hypotonia, which slowly disappeared within three years. Subsequently the children started to sit and crawl on hands and knees, improving in muscle strength and locomotion with time until they were eight years old, when they could stand up and walk upright despite severe truncal ataxia. At this stage, they also started to walk on all four extremities developing a well developed skill and balance, despite initial unskilled trials of quadrupedal locomotion. They are all skilled quadrupeds now.

Patient D1 (27 years old) had a generalized dystonia, being unable to stand up or walk without help; she could not understand the spoken language, and could not speak at all. She was born without any complication after a normal gestation period. One daughter (D2) and two sons (S1, S2) exhibited the whole spectrum of the symptoms of UTS: habitual quadrupedal locomotion, no speech, and mental retardation with no conscious experience. The results of the neurological examinations were presented in Illustration 3. The brain MRI scans of the siblings affected with UTS showed cerebello-vermial and ponto-medullar hypoplasia with additional gyral simplification on the cerebral cortex (Illustration 4), whereas the MRI of the eldest daughter (D1) with severe dystonia did not show any abnormality.

The youngest of the affected siblings (S2) could not stand up without help, but walked easily and effectively on all four extremities. The young man (S1) and the young woman (D2) could easily stand up and walk back and forth, despite truncal ataxia, but to walk around, they used habitual quadrupedal locomotion, with great ease and no signs of imbalance. During walking, they exhibited diagonal-sequence quadrupedal gait (see video). They could understand most of the spoken language, but not express themselves, using only a few sounds instead of words. All of the affected cases were mentally impaired, and it was impossible to establish a contact with them to perform an intelligence test.

Discussion

We presented a new family with consanguineous parents with five siblings, three of them exhibiting UTS (two sons (22 and 10y) and one daughter (19y)), with late childhood quadrupedalism. A fourth sibling, a daughter (27y) was completely disabled in the psychomotor domain. Interestingly, for the first three years of their lives the UTS-affected children showed a severe postnatal hypotonia: they could not move, always lying on their backs (supine position). During these three years there were tiny improvements in the efficiency and vitality of their locomotor system, and the hypotonia progressively disappeared. By the time they were three they could sit without help and started to crawl on hands and knees. They could not stand up and walk upright because of the severe truncal ataxia, but this improved progressively and at the age of eight they had started to stand up and walk upright despite ataxia. At around the same time they began to move around on all four extremities, clumsily at first, but improving as they developed more strength.

So, we see here another variant of UTS, showing slowly emerging quadrupedalism over several years, depending upon the activity of the adaptive self-organizing dynamical system [see 12]. Among others (genetics, neural networks, central pattern generators, rewiring, muscles, hormones, family, imitation, and so on) the environmental factors, such
as an uneven, hilly landscape, were important elements for the emergence of the late childhood quadrupedalism during the process of adaptive self-organization occurring within the main dynamic system [12].

This is the second report of late childhood quadrupedalism, but the previously reported case had no postnatal hypotonia [10]. The cases with late onset quadrupedalism may not be considered distinct clinical entities, but rather may be UTS variants. Similar to these UTS cases with progressive improvement, there were other non-progressive cerebellar ataxias with progressive improvement of coordination and ataxia occurring over the course of many years [14-17].

Non-progressive cerebellar ataxias with psychomotor developmental delay and autosomal recessive inheritance were reported at least as early as 1905 [18]. This condition, with hypotonia, dysmetria, unsteady gait, and marked intention tremor was designated as “disequilibrium syndrome” (DES) [19, 20]. The same condition was later described in Hutterites in Canada. The Hutterites had consanguineous parents, and exhibited postnatal hypotonia, psychomotor developmental delay, unsteady, broadly based gait and stance, exaggerated deep tendon reflexes mainly in the lower extremities, and mild to moderate mental retardation. Their condition was classified as DES [21]. A similar condition, “Cayman ataxia,” was also discovered in an isolated population from the Cayman Islands [22, 23].

The cases presented in the current work seem to be similar to the DES or Cayman ataxia, at least in their early childhood symptoms, but they develop the symptoms of UTS in late childhood, with the primary locomotor characteristic of habitual quadrupedalism, which may be designated as “late onset UTS”. This does not exclude UTS as a distinct entity among the congenital autosomal recessive cerebellar ataxias, since many syndromes share multiple symptoms [see 12]. In accord, “most of the proposed classification — of non-progressive cerebellar ataxias — in the literature is based on the adult population and pediatric aspects are only discussed in a limited way” [24]. Moreover, “in children with non-progressive cerebellar dysfunction, cerebellar symptoms may change depending on the stage of general motor development, improving with maturation of the motor system.” [24]. For these reasons, the emergence of a late onset UTS is reasonable.

The genetic analyses of this family are being carried out by Dr. Tayfun Ozcelik and his co-workers in the Department of Genetics and Molecular Biology at Bilkent University, Ankara. We do not think a single mutation would be enough to explain the origins of UTS, considering the principles of the adaptive self-organization, which states that a single gene or genes cannot be the primary source of normal or pathological behavior. Instead, the origins lie in many dynamically interacting subsystems, such as central pattern generators, joint synchrony, posture, balance, body constraints, muscle strength, extensor and flexor motor systems, perceptual processes, cognition, motivation, imitation, and environment [see 12]. In this context, Maher [25] stated in an interesting article published in Nature: “even when dozens of genes have been linked to a trait, both the individual and cumulative effects are surprisingly small and nowhere near enough to explain earlier estimates of heritability.” Moreover, Steve Jones, Professor of Genetics at University College London argued that the current direction of genetics research “is just plain wrong...The mountain has labored and brought forth not much more than a mouse” [26].

Conclusion(s)

We presented here three new cases with late onset UTS, residing in the middle region of Anatolia. These cases were considered a new variant of UTS, that is, late onset UTS with postnatal hypotonia, emerging from the adaptive self-organization among many subsystems interacting with each other within a dynamic system, after a long-lasting incubation period of many years. The late onset UTS was considered as a distinct entity among many other non-progressive autosomal recessive cerebellar ataxias, such as Cayman ataxia and disequilibrium syndrome, considering the considerable overlap of symptoms of closely related syndromes. Concerning genetics, the minor role of gene(s) in the origin of diseases including UTS was accentuated.

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Authors Contribution(s)

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Reference(s)

11. Tan U. Two new cases of Uner Tan syndrome: one man with transition from quadrapedalism to bipedalism; one man with consistent quadrapedalism. WebmedCentral Neurology2010; 1(9): WMC00645.
Illustrations

Illustration 1

Families with Uner Tan syndrome hitherto found in Turkey

<table>
<thead>
<tr>
<th>Families</th>
<th>Location</th>
<th>Cons.</th>
<th>N(_{\text{total}})</th>
<th>N(_{\text{UTS}})</th>
<th>N(_{\text{case}})</th>
<th>Hypotonia</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A [1-4]</td>
<td>Iskenderun (South TR)</td>
<td>Yes</td>
<td>19</td>
<td>5</td>
<td>1</td>
<td>No</td>
<td>Cerebello-vermial hypoplasia, gyral simplification</td>
</tr>
<tr>
<td>B [4-6]</td>
<td>Adana (South TR)</td>
<td>Yes</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>C [7]</td>
<td>Gaz/ Antep (South TR)</td>
<td>Yes</td>
<td>30 in 5 families</td>
<td>7</td>
<td>-</td>
<td>No</td>
<td>Cerebello-vermial hypoplasia, gyral simplification</td>
</tr>
<tr>
<td>D [8]</td>
<td>Canakkale (North TR)</td>
<td>Yes</td>
<td>9 in 2 families</td>
<td>4</td>
<td>-</td>
<td>No</td>
<td>Cerebello-vermial hypoplasia, gyral simplification</td>
</tr>
<tr>
<td>E [9]</td>
<td>Adana (South TR)</td>
<td>No</td>
<td>2 in 2 families</td>
<td>2 (fac. QL)</td>
<td>-</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>F [10]</td>
<td>Adana (South TR)</td>
<td>No</td>
<td>5</td>
<td>1 (late QL)</td>
<td>-</td>
<td>No</td>
<td>Cerebello-vermial hypoplasia</td>
</tr>
<tr>
<td>G [11]</td>
<td>Kars (East TR)</td>
<td>Yes</td>
<td>6</td>
<td>1 (con. QL)</td>
<td>1 QL to BLP</td>
<td>case1: no, case2: yes</td>
<td>Cerebello-vermial hypoplasia</td>
</tr>
</tbody>
</table>

Cons: consanguineous family; N\(_{\text{total}}\): number of children; N\(_{\text{UTS}}\): number of cases with UTS; N\(_{\text{case}}\): number of cases exhibiting no UTS despite truncal ataxia; TR: Turkey; Hypotonia refers only to postnatal hypotonia.
Illustration 2

Pedigree with consanguineous parents; arrows show the patients with Uner Tan syndrome; circles, females; squares, males
Illustration 3

Results of neurological examinations

<table>
<thead>
<tr>
<th>Examinations</th>
<th>Case D2</th>
<th>Case S1</th>
<th>Case S2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tandem walk</td>
<td>Impossible</td>
<td>Impossible</td>
<td>Impossible</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>Postnatal</td>
<td>Postnatal</td>
<td>Postnatal</td>
</tr>
<tr>
<td>Muscle tone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper extremities</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Lower extremities</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Muscle power</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper extremities</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Lower extremities</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Tendon reflexes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper extremities</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Lower extremities</td>
<td>Hyperactive</td>
<td>Hyperactive</td>
<td>Hyperactive</td>
</tr>
<tr>
<td>Babinski sign</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Left</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Strabismus</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Pes planus</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Finger-to-nose-test</td>
<td>Mildly clumsy</td>
<td>Mildly clumsy</td>
<td>Mildly clumsy</td>
</tr>
<tr>
<td>Heel-to-shin-test</td>
<td>Mildly clumsy</td>
<td>Mildly clumsy</td>
<td>Mildly clumsy</td>
</tr>
<tr>
<td>Altern. movements</td>
<td>Clumsy</td>
<td>Clumsy</td>
<td>Clumsy</td>
</tr>
</tbody>
</table>
Illustration 4

MRIs: left, sagittal; right, coronal; above, normal subject; below: the patient with UTS
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