
Two New Cases of Uner Tan Syndrome: One Man with Transition from Quadrupedalism to Bipedalism; One Man with Consistent Quadrupedalism

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Abstract

Background: Uner Tan syndrome, first described in 2005, consists of three main symptoms: habitual locomotion on all four extremities, impaired intelligence, and dysarthric or no speech. This extremely rare syndrome shows an autosomal recessive inheritance due to consanguineous marriages between parents. In general, there is a cerebellovermial hypoplasia with a mild gyral simplification in the cerebral cortex. Truncal ataxia is the main neurological finding, causing difficulty in standing and upright walking on two legs.

Methods: As soon as the new cases came to light, the family was visited. After taking the basic information about the family members, the traditional neurological examinations were performed, MRI scans of the patients and of a healthy family member were taken in a hospital nearest to the residence (a small village near Kars, Turkey). The patients were also filmed to analyze their walking patterns.

Results: Two individuals (case 1, 44y; case 2, 43y) among six siblings from a family with consanguineous parents exhibited Uner Tan syndrome, with quadrupedalism, impaired intelligence, and dysarthric speech. Their pedigree suggested an autosomal recessive inheritance. MRI scans showed inferior cerebellovermial and pontobulbar hypoplasia.

Case 1 did not display hypotonia, while case 2 had been hypotonic for two years after birth. Case 2's hypotonia progressively disappeared, and at three years old he started to sit, and could walk on all fours by the age of four. Case 1 was quadrupedal for 20 years, and then walked upright with the aid of a walking stick. Tendon reflexes were normal in case 1 but hyperactive in the lower extremities of case 2; Babinsky was absent in case 1 but bilaterally present in case 2. There was no nystagmus, no strabismus, and no pes pedus in either case. Cognition was severely impaired in both.

Conclusion: The emergence of quadrupedalism during development, with a transition into bipedalism in case 1, and the emergence of the quadrupedalism after a full hypotonia and no locomotion in case 2, were considered as examples of the processes of adaptive self-organization, from the viewpoint of dynamic systems theory.

Introduction

In 2005, I first described a new syndrome with the three main symptoms of habitual quadrupedal locomotion on four extremities, impaired intelligence, and dysarthria, in five cases among 15 siblings residing in a small village near Iskenderun (southern Turkey [1-4]. Following the discovery of the syndrome, also called Unertan syndrome or UTS [1], I found two further quadrupeds from two families residing in Adana, southern Turkey [5-6], six patients from two families living in a small village near GaziAntep, southern Turkey [7], and four patients from two families residing in a small village near Canakkale, northern Turkey [8]. Beside these 17 published cases with fully developed symptoms of UTS, I have discovered seven more cases residing in two small villages, also in southern Turkey (Tan, unpublished observations).

The patients with UTS did not exhibit any childhood hypotonia, and the parents are not sure if their children crawled on hands and knees or on hands and feet (bear crawling). They generally do not remember if there was a transition from hands-knees crawling to hands-feet crawling or if they directly showed bear crawling, but they are all sure their children could not stand up and walk upright, and instead they all preferred bear crawling, and otherwise were strong and dynamic, lively children, with no hypotonia. They could not walk upright, but instead ran around on four extremities with great ease and skill. This is the most remarkable feature differentiating UTS from disequilibrium syndrome [9] and Cayman ataxia [10], which are always associated with an extensive childhood hypotonia, and therefore with almost no

locomotion at all. (See Tan [4] for a more detailed comparison.)

The habitual locomotion on all four extremities is the quintessential symptom of UTS, i.e., “*homo quadrupedus*” with impaired intelligence. However, I have also found two bright children (four and eight years old) with no neuropsychological signs or symptoms except a bilateral positive Babinsky sign and inability to stand on one leg. Interestingly, these children ran on all four extremities for fast locomotion, but otherwise preferred bipedal locomotion for everyday activities, i.e., they showed *facultative quadrupedalism* [11]. Moreover, some adults with a paralyzed leg due to childhood poliomyelitis have also been discovered with a preference for quadrupedal locomotion, rejecting any measure to walk upright. These rare cases were also quite normal neuropsychologically, with a normal brain MRI [4, 12]. Apparently, these quadrupedal cases cannot be included in the syndrome, since UTS is a symptom complex that includes cognitive decline. The patterns of facultative quadrupedal locomotion on all four extremities or palmigrade walking on all three extremities with a paralyzed leg may be due to emergent motor patterns resulting from the process of self-organization during motor development of children, considered in the dynamic systems theory [4, 13].

The early cases exhibiting UTS started to walk on all four extremities — as a result of adaptive self-organization to more or less impaired balance — in early childhood at around one to two years of age. However, I have found a 12-year-old boy who started to walk on all four extremities at 10 years of age, after years of ataxic bipedal walking. This case exhibited the full spectrum of symptoms of UTS, i.e., habitual quadrupedalism, impaired intelligence, and no speech [14]. “*Apparently, the patient’s motor system was prepared during the first ten years to run economically on all four extremities, and the slow, uneasy, ataxic, upright gait was replaced by rapid, easy, and well-balanced quadrupedal gait... It took 10 years for rewiring of the motor system to create a new walking style. This suggests that an adaptive self-organization within the nervous system may take a long time to establish a novel locomotion*” [14]. In the present work I will present two novel cases exhibiting further variants of UTS with late onset ataxic bipedalism and early onset quadrupedalism.

Methods

The participants were two men, 43 and 44 years old,

exhibiting the symptoms of the Uner Tan syndrome. As a routine neurological examination, the neurologist looked for horizontal and/or vertical nystagmus. Truncal stability during sitting and standing was examined to assess the spinocerebellar system. The cranial nerves, muscle tone, muscle strength, coordination, gait, rapid alternating movements, finger-nose and heel to shin tests, deep tendon reflexes, clonus, plantar response (Babinsky), and position senses were all examined.

Following neurological examinations, the patients were transported to the radiological Department of Governmental Hospital in Digor, Kars. Patients’ heads were scanned with a 0.3 T magnetic resonance scanner using coronal and sagittal sequence. The patients were request to remove anything that might degrade images of the head. After positioning the individuals on a sliding table, the radiologists left the room and MRI sequences were performed.

Results

The cases were two brothers from the same family with consanguineous parents who were first cousins, i.e., first degree relatives. The pedigree of the family is presented in Illustration 1. The mother was 65 years old, and the father died of cancer at 60 years of age. Two daughters were fraternal twins (F1, F2). The results of the neurological examinations are presented in Table 1.

Case 1 (M1 in Illustration 1) was a 44 year old man born by uncomplicated delivery following a normal gestation period. After a normal crawling period on hands and knees, he started to walk on all four extremities on hands and feet because of truncal ataxia. His height, weight, and head circumference were within normal limits. His cognitive abilities were severely impaired, with no conscious experience. The expressive speech was not understandable (slurred speech), and he could understand only simple commands. The patient could not name objects, did not know the date, and was unaware of his name, the president’s name, or the names of his village, city, or country. He had no short-term memory for objects, he could not repeat numbers, and could not count from one to five. He could stand up and remain upright with eyes open or closed, and could walk upright, but only with great difficulty due to truncal ataxia.

Case 2 (M2 in Illustration 1) was also born of an uncomplicated delivery after a normal gestation. He was hypotonic after birth for two years, progressively

improving by the age of three, by which time he could sit down by himself. After a crawling period on hands and knees, the hypotonia disappeared, and he started to walk on all four extremities at the age of four years. He cannot stand up without help, and can only walk on all four extremities, which he does with well developed balance, great ease, and speed. His gait showed the characteristics of a diagonal-sequence quadrupedal locomotion (see video 1). His brain MRI showed cerebellovermial and pontobulbar hypoplasia in the sagittal and coronal sections (see Illustration 2). His height, weight, and head circumference were within normal limits, but cognitive abilities were severely impaired, including conscious experience. The patient was unaware of his name, place, date, city, or country; he had no short-term memory, did not understand numbers (could not count from one to five), and he could understand only simple commands.

Discussion

In the present work, I have presented two cases exhibiting the three main symptoms of Uner Tan syndrome: quadrupedal locomotion, impaired intelligence, and dysarthric speech [1, 2, 4]. The pedigree suggested an autosomal recessive inheritance due to consanguineous marriage between parents, (found in almost all cases exhibiting UTS). Case 1 had been a lively child during postnatal development, but could not stand up following crawling on hands and knees, and instead started to crawl on hands and feet at about two years of age. So, his locomotor development did not go further and stopped at this stage, i.e., crawling on all four extremities.

Contrary to the case 1, case 2 was hypotonic just after birth, which lasted for about four years. He could sit, however, by about three years of age, and showed an improvement during motor development. At four years of age he started to walk on all four extremities, being unable to stand up due to the severe truncal ataxia. Interestingly, case 1 started to walk upright, albeit with truncal ataxia, using a walking stick after 20 years of walking on all fours. Case 2 has not changed his locomotion on all four extremities, during his 43 years. Case 1 and 2 both showed progressive improvement in locomotor function, with case 1 exhibiting a transition from quadrupedality to bipedality, and case 2 from childhood inability to move due to severe hypotonia, to starting to sit and walk on all four extremities with normal muscle tone.

The development of the locomotor functioning in both cases, one of them being unable to stand up due to

severe truncal ataxia, but, instead, starting to easily and effectively walk on all fours during childhood, with a transition from habitual quadrupedal walking to habitual bipedal walking at about 20 years of age, the other being unable to move at all due to the childhood hypotonia, but later being able to sit and then to walk on all fours without hypotonia, are examples of adaptive self-organization, according to the dynamic systems theory, which states: "*stepping and, ultimately, walking are not innate or prescribed. Rather, they are self-organized and emergent, reflecting an assembly of multiple subsystems within the infant's history of activity in context*" [15]. Self-organization is a "*reorganization that alters a system in an adaptive fashion when it is subjected to new constraints*" [16].

The genetic analysis for cases 1 and 2 is being performed by Tayfun Ozcelik and his co-workers in Bilkent University, Ankara. This takes a long time and is not completed yet. UTS can be considered within the framework of the non-progressive autosomal recessive cerebellar ataxias, which have been shown to be associated with several genetic mutations [4]. Likewise, UTS was also shown to be associated with several genes, being a syndrome with genetic heterogeneity [17]. There are indeed overlapping symptoms among cerebellar ataxias. In this context, Cayman ataxia [18] and Disequilibrium syndrome (DES-H) are not essentially different from each other, both being associated with truncal ataxia, hypotonia, psychomotor delay, dysarthria, and cerebellar hypoplasia [19]. Among the non-progressive cerebellar ataxias, Uner Tan syndrome, with the quintessential symptom of the habitual quadrupedal locomotion, as a distinct entity, is discussed in detail elsewhere [4].

The effects of genetic mutations can be complex and different mutations in a single gene may lead to different expressions of the same phenotype: "*similar genetic lesions can have entirely different phenotypes*" [20]. So, in the context of the genetic heterogeneity of many syndromes like UTS, genetics alone do not seem to be informative for the origins of a syndrome. Indeed, Ewing and Green [21] estimated the number of human genes to be approximately 35,000, but this cannot be sufficient for the complexity of the human nervous system to be hard-coded in the genome [22]. Accordingly, the functions of the neural circuits cannot be determined only by genes [23]. In view of this, the traditional theory of the development of the locomotor system as a gradual increase of the cortical motor system is now replaced by the dynamical systems theory (any system that changes over time): motor behavior emerges from the dynamic interactions of

many subsystems, which self-organize to produce locomotion, and which do not depend on the prior existence of instructions embedded within the central nervous system or genetic codes [24]. Accordingly, Tan [4] stated: *“from the viewpoint of dynamic systems theory, there may not be a single factor that predetermines human quadrupedalism in Uner Tan syndrome, but it may involve self-organization, brain plasticity, and rewiring, from the many decentralized and local interactions among neuronal, genetic, and environmental subsystems.”*

Uner Tan syndrome sparked world-wide interest [25, 26, 27, 28, 29]. Two interesting and rather comprehensive articles by Greg Downey, Senior Lecturer in Anthropology at Macquarie University in Sydney, were published about UTS in the recently introduced PLoS blog Neuroanthropology [30, 31]. Moreover, the human quadrupedalism, “homo quadrupedus”, UTS was considered a phenotypic example of evolution in reverse [4], i.e., *“the reacquisition of the same character states as those of ancestor populations by derived populations”* [32]. On the other hand, Tan [4] suggested that *“UTS may be considered within the framework of phylogenetic diseases [28] associated phylogenetic regression [33], and this may in turn be related to the theory of human backward evolution”* [4].

Conclusion(s)

Two new cases exhibiting the three main symptoms of Uner Tan syndrome (habitual quadrupedal locomotion, impaired intelligence, dysarthric speech) were presented in the present work. Their pedigree suggested an autosomal recessive inheritance, with their parents being first cousins. The cases were considered among the recessive non-progressive spinocerebellar ataxias. The locomotor system showed a progressive improvement: there was a transition from quadrupedalism to bipedalism in case 1, and the childhood hypotonia in case 2 progressively disappeared within two years, to be replaced by quadrupedal locomotion. MRI scans showed hypoplasia in the inferior cerebellum and vermis. The emergence of quadrupedalism after a full hypotonia and no locomotion in case 2, and the emergence of the quadrupedalism during development with a transition into bipedalism in case 1 were considered to be processes of adaptive self-organization, from the viewpoint of dynamic systems theory.

It has been proposed that UTS may be considered a phenotypic example of evolution in reverse, within the

framework of phylogenetic diseases. Moreover, the transition from quadrupedalism to bipedalism within a long-lasting self-organization period in case 1 nicely reflects the gradual transition from homo quadrupedus to homo erectus during human evolution.

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Authors Contribution(s)

Uner Tan found and visited the family, examined the patients, designed, analyzed the results, and wrote the paper.

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Illustrations

Illustration 1

Pedigree of the Family of Case 1 and Case 2.

Illustration 1

Pedigree of two affected men exhibiting Uner Tan syndrome with habitual quadrupedal locomotion (M1, M2). Circles represent females, while squares present males; crossed symbols: deceased members. Dates are the years of birth.

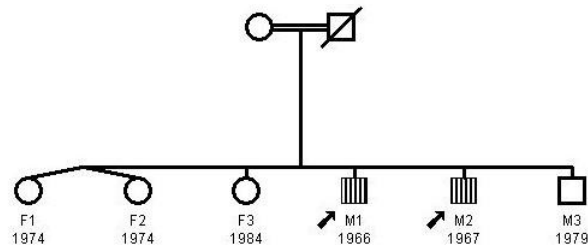


Illustration 2

Table "Characteristics of two cases exhibiting Uner Tan syndrome"

Illustration 2

Characteristics of two cases exhibiting Uner Tan syndrome

Examinations	Case 1 (M1)	Case 2 (M2)
Sex	Male	Male
Age	44	43
Gait	Quadrupedal for the first 20 years, now biped ataxic	Habitual diagonal-sequence quadrupedal locomotion
Standing up	Possible with difficulty	Impossible without help
Tandem walk	Impossible	Impossible
Upright walk	Ataxic, using walking stick	Impossible
Hypotonia	Absent	Present for two years
Muscle tone		
Upper extremities	Normal	Normal
Lower extremities	Normal	Normal
Muscle power		
Upper extremities	Normal	Normal
Lower extremities	Normal	Normal
Truncal ataxia	Present, not too severe	Present, severe
Tendon reflexes		
Upper extremity	Normal	Normal
Lower extremity	Normal	Hyperactive (+++)
Babinsky	Absent	Present bilateral
Nystagmus	Absent	Absent
Strabismus	Absent	Absent

Pes pedus	Absent	Absent
Finger-nose	Not bad, but slow,	Not bad, but slow
Heel to shin	Not bad, slow	Not bad, slow
Alternating movements	Not good	Not good
Speech	Dysarthric	Dysarthric
MRI	Cerebellar hypoplasia, Mild gyral simplification	Cerebellar and pontobulbar hypoplasia
Microcephaly	Absent	Absent
Cranial nerves	Normal	Normal
Seizure	Absent	Absent

Illustration 3

Case 2 Brain MRI Scans

Illustration 3

Coronal (left) and sagittal (right) MRIs from the unaffected brother (A, B) and the index patient (C, D); notice the cerebellar and pontobulbar hypoplasia in the patient (C, D).

