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Üner Tan Syndrome: Review and Emergence of Human Quadrupedalism in Self-Organization, Attractors and Evolutionary Perspectives

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1. Introduction

1.1 History and clinical features

The first man reported in the world literature exhibiting habitual quadrupedal locomotion was discovered by a British traveler and writer on the famous Bagdad road near Havsa/Samsun on the middle Black Sea coast of Turkey (Childs, 1917). The man most probably belonged to a Greek family, since the region of Havsa was populated by Greek people during the time of the Ottoman Empire. He possibly belonged to a consanguineous family resident within the closed Greek population, which had a high probability of interfamilial marriages. Childs described this man in his book (p.29) as follows:

"As we rose out of the next valley a donkey and a figure on the ground beside it attracted my attention. They were in the shadow of a solitary tree growing at the roadside. The donkey stood with drooping head, the picture of patience, but the figure moved in a curious fashion, and I went up to look more closely. And now it appeared that I had fallen into the trap of a beggar, one of those mendicants who infest the road and profit by their infirmities. He sprang up and asked for alms, and because these were not immediately forthcoming went on all fours and showed a number of antics, imitating a dog and goat and other animals to admiration. Then I saw he was without thighs; that the knee-joint was at the hip, the leg rigid, and only half the usual length. With his grim bearded face thrust upwards, and the odd movements of his little legs, he lacked only a stump of tail to make me think I had come upon a satyr in life. At last I photographed him, and gave him three piastres for his trouble."

This man can be considered as the first case in the world literature exhibiting Uner Tan syndrome (UTS) with habitual locomotion on all four extremities (quadrupedalism), mild or severe mental impairment, and dysarthric or no speech (see the review Tan, 2010a). The most impressive symptom of UTS, the habitual quadrupedal locomotion, is consistent with the man seen by Childs, while the other two symptoms, mild mental impairment and no expressive speech, can be inferred from the sentence "*He sprang up and asked for alms, and because these were not immediately forthcoming went on all fours and showed a number of antics,*

imitating a dog and goat and other animals to admiration." As reported by Tan (2010a), the UTS cases occur in consanguineous families, and the closed population the man probably belonged to suggests the possibility of such interfamilial marriages. Moreover, the man was a beggar similar to most of the contemporary quadrupeds discovered in Turkey. Childs argued that the man had no thighs, the knee joint being at the hip. This seems, however, not to be true, and the differences seem instead to be due to heavily stretched legs as usually seen in UTS cases. Another interesting feature of the Child's quadruped man is the relatively high arm to leg ratio (92.0%) compared to the arm to leg ratio of 90.0% in one case exhibiting UTS in an Adana family (Tan, 2006b, c). Fig. 1 shows the quadruped man with his donkey (top) on the hill beneath the famous Bagdad road (bottom) photographed by Childs (1917).

Beggar of the Bagdad Road.

Traffic on Bagdad Road, near Khassa.

Fig. 1. Man with habitual quadrupedal locomotion with his donkey at the top of a hill (top) beneath the famous Bagdad Road (bottom) during the Ottoman Empire period (from Childs, 1917).

Interestingly, no single case with human quadrupedalism was reported in the scientific literature after Childs' first description in 1917 until the first report on the Uner Tan syndrome in 2005 (Tan, 2005a-d). The novel syndrome was first found in a consanguineous family with 19 siblings living in Iskenderun in Southern Turkey. Five of the siblings exhibited the new syndrome, with three main symptoms: habitual quadrupedal locomotion, mental retardation, and dysarthric speech with no conscious experience. Actually, these cases had been known in Turkey for many years and had attracted the curiosity of the public media. It was first reported scientifically to the members of the Turkish Academy of Sciences in Ankara and Istanbul, and published under the proposed name, "*Uner Tan Syndrome*" (Tan, 2005a-d), which sparked world-wide interest (Garber, 2008; Ghika, 2008; Akpinar, 2009; Le Fanu, 2009; Held, 2009). Two interesting and rather comprehensive articles by Greg Downey (2010a, b), Senior Lecturer in Anthropology at Macquarie University in Sydney, were published about UTS in the recently introduced PLoS blog Neuroanthropology. Pribut (2010) also reported that this syndrome was first discovered in 2005 by Üner Tan of Cukurova University in Turkey, who is also a member of the Turkish Academy of Sciences.

Between 2005 and 2010, 10 families exhibiting the syndrome were discovered in Turkey, with 33 cases: 14 women (42.4%) and 19 men (57.6%), (see Table 1). The Diyarbakir family actually consisted of two subfamilies (DI 1-2).

In addition to the cases in Table 1, two male children belonging to two different families resident in Adana and Istanbul were further reported with respect to human quadrupedalism (Tan & Tan, 2009). Interestingly, these children, 4 and 12 years of age, exhibited facultative quadrupedalism but did not show neurological or psychological signs and symptoms. They preferred upright bipedal gait for everyday, medium-speed actions, but preferred locomotion on all four extremities for fast actions, such as playing with children or hurrying to somewhere else. Apart from these cases in Turkey, four brothers with UTS from a consanguineous family were reported in Brazil (Garcias & Martino, 2007), and two adult men from Iraq (Turkmen et al., 2009). Additionally, one adult man from Mexico and one adult man from Chile were also reported by e-mail communication. Altogether, the number of total cases increased to 39, being 25 men and 14 women (not including those reported by email). That is, the cases exhibiting the syndrome hitherto discovered around the world were 35.9% women and 64.1% men. Statistical analysis showed that the number of men significantly exceeded the number of women exhibiting the syndrome (χ^2=5.12, df=1, $p < .05$).

The results are summarized in Table 1, which presents families discovered in Turkey exhibiting Uner Tan syndrome. Of the 33 cases, 10 cases (30.3%) had early-childhood (postnatal) hypotonia, which disappeared during late childhood. The mean age for starting to walk on all four extremities was 3.9±2.1 years (n=33; range=8.0 years, minimum age=2.0, and maximum age=10). Except for one case in the Adana1 family, all of the cases could stand up and walk without assistance despite great difficulty due to truncal ataxia. Some of the patients could even walk forwards and backwards without assistance, despite truncal ataxia. However, all of them could walk around on all four extremities easily without any discomfort, and even faster than biped individuals, as if this gait were their natural locomotion.

Families	ISK	AD1	ANT	CAN1	CAN2	KA	AFY	AD2	DI 1-2
Consang.	Yes	No	Yes	No	No	Yes	Yes	No	Yes
N	19	3	29	2	2	2	3	5	22
Men	8	2	16	1	1	2	2	4	13
Women	11	1	13	1	1	0	1	1	9
Age	19-35	27-33	12-46	62-65	22	43-44	10-22	12-21	3-30
N (QL)	6	2	7	2	2	2	3	1	7
Men	2	1	5	1	1	2	2	1	4
Women	4	1	2	1	1	0	1	0	3
Age	19-33	27-37	12-46	62-65	22	43-44	10-22	12	7-25
N BL-atax	1	1	0	0	0	0	0	0	2
Men	1	1	0	0	0	0	0	0	1
Women	0	0	0	0	0	0	0	0	1
Age	33	43							14-21
Locus	WDR81	Ch.13q	vldlr	vldlr	vldlr	(?)	(?)	(?)	(?)
Vest.imp.	Central	Periph.	Central	Central	Central	Central	Central	Central	Central
Cerebellum	Hypo.	Normal	Hypo.	Hypo.	Hypo.	Hypo.	Hypo.	Hypo.	Hypo.
Vermis	Hypo.	Normal	Hypo.	Hypo.	Hypo.	Hypo.	Hypo.	Hypo.	Hypo.
Cereb.cor.	Simp.gyri	Normal	S.gyri	S.gyri	S.gyri	S. gyri	S.gyri	Norm.	S.gyri
DTR upp.	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Hypo.	Norm.
DTR low.	Hyper.	Hyper.	Hyper	Hyper	Hyper.	Hyper.	Hyper.	Hypo.	Hyper.
Muscle Tone	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Strength	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Babinski	+(3/5)	Absent	+(3/7)	Absent	Absent	+ (1/2)	+(1/3)	Absent	+(1/7)
Tremor	Mild	Mild	+(1/7)	No	No	No	No	Yes	No
Nystagmus	Yes	Yes	No	No	No	No	No	No	2/3
Early Hyp.	No	No	No	No	No	1/2	Yes	No	Yes
Understand	Some	Some	Some	Some	Some	Some	Some	Some	Some
Speech	Dysar.	Dysar.	No	No	No	Dysar.	No	No	No
Truncal ataxia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Standing	Yes	No	Yes	Yes	Yes	Yes	2/3	Yes	2/3
Bipedal walk	Ataxic	No	Ataxic	Ataxic	Ataxic	Ataxic	2/3	Yes	2/3
Habit. QL	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Facul.	Yes
Age QL	3-4 year	2-3 year	2-4 year	2-4 year	2-4 year	3-4 year	6-8 year	10 year	6 year

Families: ISK: Iskenderun, AD1: Adana1, ANT: GaziAntep, CAN1: Canakkale1, CAN2: Canakkale2, KA: Kars, AFY: Afyon, AD2: Adana2, DI 1-2: Diyarbakir 1 and2. Consang.: consanguinity; QL: quadrupedal locomotion; BL: bipedal locomotion; atax.: ataxia; Vest. imp.: vestibular impairment; cereb.cor. cerebral cortex; DTR: deep tendon reflex, upp.: upper extremity, low: lower extremity; hypo.: hypotonia; hyper.: hypertonia; exp.: expressive; habit.: habitual.

Table 1. Families with Uner Tan syndrome hitherto discovered in Turkey

The cases in three families showed dysarthric speech (n=10/33, 30.3%), and the remaining 23 cases (69.7%) had no speech at all except one or two nonsense sounds. The number of cases with no speech significantly exceeded the number of cases with dysarthric speech (χ^2=8.73, df=1, $p < .005$). However, all of them could understand simple questions and commands (go, walk, come, eat, etc.). The dysarthric cases had very limited vocabulary, and could not name simple objects such as shoe, house, car, dog, cat, chair, etc., and they had no idea at all about abstract words. They could not make sentences using "and" or "with."

1.2 Cognition

The patients' cognitive abilities were assessed by the "Mini Mental State Examination Test," also known as the "Folstein test" (Folstein et al., 1975), which consists of a 30-point questionnaire, and is commonly used in medical clinics, especially to screen for dementia. The test measures the individual's orientation, attention, calculation, recall, language and motor skills. The total possible score is 30 points, with equal or greater than 25 points being normal, 21-24 indicating mild mental impairment, 10-20 points moderate, and below or equal to 9 severe (Mungas, 1991). According to the results presented in Table 2, all of the cases with dysarthric speech showed severe mental retardation (range=0 to 2 points), the remaining cases with no speech but a simple sound were even worse in cognitive abilities, so that no contact could be established with them. They could not perform the reading and writing items because all of the patients were illiterate. The healthy, but illiterate, siblings of the affected individuals were relatively good in the mini-mental-state examination test; with scores ranging between 25 and 29 points (mean=27.1±2.2), although they shared the same environment. In cases from Adana, Iskenderun, and Diyabakir familes (n=10), the Wais-R (Wechsler Adult Intelligence Scale-Revised, Wechsler 1997) was used to assess IQ, which ranged from "0" to "4" of a total 30 points. This test also indicated a severe mental retardation in these cases with the syndrome.

Questions	Patients' answers
What is today's date? What is the month? What is the year? What is the day of the week today? What season is it?	*Orientation to time:* They gave unrelated answers such as 80, 90, animal, July, house, cow, dog, etc., or did not give an answer at all.
Whose house is this? What room is this? What city are we in? What country are we in?	*Orientation to place:* Nobody could give a correct answer, or they replied with unrelated words such as summer, me, winter, animals, mother, etc.
Immediate recall, repeat: Ball, flag, tree	Nobody could recall any of these words.
Attention: Count backwards from 100 by 7	Nobody could count backwards, and they could not count forwards from zero to ten.
Delayed verbal recall: Recall 3 words I asked previously	Nobody could recall the words previously asked.
Naming: (watch, pencil)	Nobody could name these objects.
Repetition: Repeat following: No if, ands, or buts	Nobody could repeat them.
3-stage command: "The the paper in your hand, fold it in half, and put it on the floor."	Nobody could follow the command, and none could even take the paper in their hands.

Table 2. Questions from the Mini Mental State Examination Test and Patients' Answers

Neurological examination found nystagmus in 10 of the 33 cases (30.3%). All of the cases showed severe truncal ataxia. Babinski sign was present in nine cases (27.2%). The muscle tonus was normal with strong legs and arms in all of the cases. The deep tendon reflexes were normal in the upper extremities, except in one case in the Adana2 family, who had hypoactive tendon reflexes, being hyperactive (without clonus) in the lower extremities. Magnetic resonance imaging (MRI) scans of the cerebral cortex showed mildly simplified gyri in eight families (n=25, 75.6%), and were normal in two families. There was cerebello-vermial hypoplasia in nine families, but normal in one case in the Adana family (Fig. 2). Barany's caloric nystagmus test showed peripheral vestibular impairment in one family (Adana1), but central vestibular impairment in the remaining nine families.

Fig. 2. MRIs: above left, no vermial hypoplasia, quadruped man from Adana1 family (below left); above right, vermial hypoplasia, quadruped man from Iskenderun family (below right).

1.3 Genetics

The genealogical analysis suggested autosomal recessive transmission linked to chromosome 17p13.1-13.3, with a missense mutation in the WDR81 gene for the cases from the Iskenderun family (Gulsuner et al., 2011). Chromosome 13q could be involved in

missense mutation in the Adana family (Tayfun Ozcelik, personal communication). Homozygocity was found in the affected cases of the Antep and Canakkale families, and this was mapped to a region on chromosome 9p24, including the very low density lipoprotein receptor gene (VLDLR) (Ozcelik et al., 2008a). These results suggest Uner Tan syndrome may be heterogeneous with regard to its genetic origins (see Tan, 2010a for a recent review). Interestingly, the mother of the affected siblings in the Iskenderun family had type-1 diabetes, and it is reported that maternal diabetes may be associated with congenital malformations and can, for instance, cause caudal regression in mice (Chan et al., 2002). Thus, the maternal diabetes could be associated with the neural damage and resulting balance disorder in the affected individuals of the Iskenderun family, in addition to the genetic defect.

2. Comparison with related syndromes

Uner Tan syndrome can be classified into two groups: Type-I and Type-II, on the basis of absence or presence of early childhood hypotonia, respectively. The main characteristics of four closely related syndromes, i.e., UTS (Type-I and Type-II), disequilibrium syndrome (DES), Cayman ataxia, and Joubert syndrome, are presented in Table 3.

Traits	UTS (TYPE-I)	UTS (TYPE-II)	DES	CAYMAN	JOUBERT
Locus (gene)	17p13(WDR81) 9p24 (VLDLR) 8q (CA8) 13q (?)	No reliable mutation in DI 1-2 family. One case in Afyon family under study.	9p24 (VLDLR)	19p13.3 (ATCAY)	8q21 (MKS3), 16q12.2 (RPGRIP1L), 6q23 (AHI1), 2q13 (NPHP1), 12q21.3 (CEP290), 9q34.3 (13 cM) 11 centrom (6 cM)
Early hypotonia	NO	YES	YES	YES	YES
Quadrupedalism	YES	YES	NO	NO	NO
Short stature	NO	NO	YES	YES	YES
Male/female ratio	2:1 (males preponderant)	2:1 (males preponderant)	1:1.75 (N=23) p>.20 (NS)	1:1 (equal sex)	2:1 (males preponderant)
Muscle tone	Normal	Normal	Decreased	Decreased	Decreased
Ambulation	Early (>2 years)	Late (>4 years)	Late (> 6 y) or no	Late, ataxic	Late (> 4 years), ataxic

Table 3. Comparison of UTS Type-I and Type-II with DES, Cayman ataxia, and Joubert Syndrome

With regard to genetics, UTS Type-I (without hypotonia) shows genetic heterogeneity: VLDLR (very low density lipoprotein receptor gene) on chromosome 9p24 in the Antep and

Canakkale families (Ozcelik et al., 2008a), WDR81 on chromosome 17p13.1-13.3 in the Iskenderun family (Gulsuner et al., 2011), locus on chromosome 13q in Adana family (Ozcelik, personal communication, the gene is not yet isolated), CA8 on chromosome 8q in the Iraqi family (Turkmen et al., 2009). UTS Type-II was representative in two families: one man of the two affected individuals in the Afyon family (Ozcelik, personal communication: genetic analysis not yet completed). Interestingly, no mutation could be identified in the Diyarbakir family; VLDLR mutation was eliminated, and even the whole Exome Sequencing did not give any reliable results (Gleenson, personal communication). Thus, UTS Type-I and Type-II seem to be genetically different, in addition to the differences in the presence or absence of early hypoptonia. However, the genetic heterogeneity seems to be a common property of almost all human genetic diseases (Ozcelik et al., 2008a). Notice that neither of the UTS types exhibited hypotonia in adulthood.

In contrast to UTS, disequilibrium syndrome (DES), first described by Schurig et al. (1981) in the endogamous North American Hutterite population, features non-progressive autosomal recessive cerebellar hypoplasia, truncal ataxia, mental retardation, short stature, hypotonia, and delayed ambulation, and is associated with a single gene, VLDLR, located on chromosome 9p24 (Boycott et al., 2005; Moheb et al., 2008). However, a re-evaluation of DES revealed no VLDLR mutations in some patients with DES who exhibited non-progressive cerebellar ataxia, dysarthria, short stature, mental retardation, and strabismus; brain MRI findings showed variations from normal to marked cerebellar hypoplasia (Melberg et al., 2011). Thus, UTS seems to be genetically different from DES in addition to the difference of hypotonia in adulthood and short stature (see Table 3).

Cayman ataxia, first discovered in the highly inbred population of Grand Cayman Island (Johnson et al., 1978), is *"a novel form of cerebellar ataxia that is not allelic to other described loci for this heterogeneous group of disorders"* (Nystuen et al., 1996), but with similar clinical symptoms to DES. Patients with Cayman ataxia exhibit marked psychomotor retardation, cerebellar dysfunction, including nystagmus, intention tremor, dysarthria, and ataxic gait, in addition to a marked cerebellar hypoplasia; hypotonia being present from early childhood (Johnson et al., 1978; Nystuen et al., 1996). The related locus is on chromosome 19p13.3, and the gene involved is referred to "*ataxia, cerebellar, Cayman type*" (ATCAY) (Bomar et al., 2003; Hayakawa et al., 2007). Thus, both DES and Cayman ataxia have entirely similar clinical features but different genetic loci and mutations. There are indeed many syndromes exhibiting genetic heterogeneity, such as Joubert syndrome (Valente et al., 2003), hereditary spastic paraplegia (Fink & Hedera, 1999), and autosomal dominant non-progressive congenital ataxia (Jen et al., 2006). Thus, the genetic heterogeneity seems to be a common property of virtually all human genetic diseases (Ozcelik et al., 2008b). These results suggest that DES and Cayman ataxia are entirely similar in phenotype, but are different in genotype. However, UTS Type-I seems to be entirely different from these two conditions with regard to genetics, hypotonia, and ambulation.

Another syndrome related to UTS, DES, and Cayman ataxia, is Joubert syndrome, first reported by Joubert et al. (1969), which features truncal ataxia, hypotonia, delayed motor development, either episodic hyperapnea or apnea, mild to severe mental retardation or normal cognition, renal disease, retinal dystrophy, and "*molar-tooth-sign*" on cranial MRIs

(Saraiva & Baraitser, 1992; Steinlin et al., 1998). At least seven loci with seven gene mutations were reported to be associated with Joubert syndrome (Parisi et al., 2004; Dixon-Salazar et al., 2004; Sayer et al., 2006; Baala et al., 2007). This syndrome shares the cardinal symptoms with DES and Cayman ataxia—truncal ataxia, hypotonia, and mental retardation—but is entirely different in genetics. With regard to Type-I and Type-II UTS, Cayman ataxia is entirely different from UTS in relation to the MRI and some cardinal symptoms.

With regard to locomotion, quadrupedalism, i.e., habitual walking on all four extremities, is the quintessence of both types of UTS, emerging during early (Type-I) or late (Type-II) childhood, depending upon gaining the muscle power necessary for quadrupedal locomotion. In contrast, ambulation with or without assistance starts during late childhood in DES, Cayman ataxia, and Joubert syndrome, because of the persistent hypotonia with weak muscles constraining locomotion. When the cases with UTS walk on all four extremities, they exhibit energetic walking with strong arm and leg muscles and even running fast on rough ground. Quadrupedalism is characteristic only in UTS Type-I and Type-II, despite truncal ataxia being also shared with all of the related syndromes. So, impaired upright balance or ataxic locomotion common to all syndromes does not seem to be the main constraint playing a role in the emergence of the habitual quadrupedal gait in UTS.

All patients of UTS Type-I and Type-II, DES, Cayman ataxia, and Joubert syndrome can understand simple commands, but they have difficulties in expressive language. In the cases with UTS Type-I (n=21), expressive speech was dysarthric in nine cases (42.9%), and there was no speech at all except one or two nonsense sounds in 12 cases (57.1%). The difference between these proportions was not significant statistically (χ^2=0.37, p>.50): the numbers of cases with only dysarthric speech and with only nonsense sounds were equal in UTS Type-I, with no significant sex difference in cases with dysarthric speech. There was also no significant sex difference in UTS Type-I cases using only nonsense sounds (n=12, males=8, females=4; χ^2=1.51, p>.20). Among the UTS Type-II cases (n=12), only one was dysarthric (8.3%), the remaining 11 cases (91.7%) had no speech at all, except one or two nonsense sounds. Concerning the total cases with no speech (n=23), in UTS Type-I and Type-II, the number of men (n=15, 65.2%) exceeded the number of women (n=8, 34.8%), the difference being marginally significant (χ^2=3.12, p=.07). On the other hand, the number of cases with no speech in UTS Type-II (n=11, 91.7%) significantly exceeded the number of cases with dysarthric speech (n=11, 18.3%) in UTS Type-II cases (χ^2=10.26, p<.001).

The number of cases with dysarthric speech in UTS Type-I (n=9 of 21) exceeded the number of cases with dysarthric speech in UTS Type-II (n=1 of 12), the difference being only marginally significant, however (χ^2=2.83, p<.10). By contrast, the number of cases with no speech in UTS Type-II (n=12 of 21, 57.14%) exceeded the number of cases with no speech in UTS Type-I (n=11 of 12, 91.67%), but the difference was statistically only marginally significant ((χ^2=2.83, p<.10). Such a statistical analysis is now available for the first time, but only for UTS, and not for the closely related syndromes.

Taken together, early hypotonia (UTS Type-II) was associated with the complete loss of the motor machinery of expressive speech, and so the patients produced nonsense sounds

instead of words. The cases without early hypotonia (UTS Type-I) could use words despite dysarthria. These results suggest a relation between early hypotonia and the development of expressive speech. Namely, the motor machinery for the fine motor skill of the tongue and oral muscles may not develop properly in Type-II cases during early childhood due to hypotonic oral muscles. Apparently, this developmental delay in motor skills for speech could not be re-gained in UTS Type-II patients despite the disappearance of the hypotonia in late childhood or adulthood. Moreover, there was a male preponderance in inability to speak in UTS cases (total sample), and more men than women had no speech in UTS Type-II cases (exhibiting early hypotonia). These results are consistent with the evidence that men have a higher incidence of impaired speech than women (McGlone, 1977; Inglis & Lawson, 1981). Such a statistical analysis of the UTS cases, considering the relation of speech ability to hypotonia, was applied for the first time in the scientific literature.

In Cayman type ataxia, speech was dysarthric (Brown et al., 1984; Nystuen et al., 1996). In DES, the patients had no speech, or dysarthric speech with limited vocabulary (Schurig et al., 1981; Glass et al., 2005; Boycott et al., 2005; Moheb et al., 2008; Mehlberg et al., 2011). In Joubert syndrome, speech was also dysarthric, but pseudobulbar in origin, despite the interpretation as a cerebellar and brainstem dysfunction (Andermann et al., 1999; Braddock, 2006). These results suggest that speech is either absent or dysarthric in all of these closely related syndromes. Only in Joubert syndrome is dysarthric speech pseudobulbar in origin, otherwise, it is cerebellar in origin in the remaining three syndromes. Despite the difficulties in expressive speech (dysarthric with limited vocabulary or no speech), all patients with UTS, DES, Cayman ataxia, and Joubert syndrome could understand simple questions or follow simple commands. Similarly, all patients with all of the above syndromes were mildly or severely impaired in cognition, i.e., they exhibited mild or severe mental retardation, with no conscious experience. However, intelligence was assessed using appropriate tests only in UTS cases, and reported for the first time in the literature. UTS was also different to the other syndromes with regard to the height of patients: there being no short stature in UTS, whereas short stature was the common characteristic of cases with DES (Glass et al., 2005; Melberg et al., 2011), Cayman ataxia (Johnson et al., 1978; Brown et al., 1984), and Joubert syndrome (Boycott et al., 2009).

Cranial MRIs of the UTS cases from the Iskenderun family showed cerebello-vermial and callosal hypoplasia, with mildly simplified cortical gyri, the basal ganglia, thalamus, bulbus, and pons being normal. However, one affected individual from Adana had a normal brain MRI, while all of the remaining cases had cerebello-vermial hypoplasia with mild gyral simplification in the cerebral cortex (Tan, Pence et al., 2008). The Barany's caloric nystagmus test, first applied to the UTS cases, indicated that the affected individuals from the Iskenderun family had a central vestibular defect, but one affected man from Adana with a normal brain MRI had only a peripheral vestibular defect (Tan, 2010a). Therefore, it is to be expected that the former cases had cortical and cerebello-vermial hypoplasia, whereas the latter had no structural anomalies in his brain. MRI showed inferior cerebello-vermial hypoplasia and simplified gyration of the cerebral hemispheres in DES, but the MRIs of the brain showed a range from normal to severe cerebello-vermial hypoplasia in UTS (Tan, 2010a). A normal brain MRI was indeed not always indicative for the clinical picture. For instance, a normal brain MRI has been found in some cases exhibiting the main symptoms of DES: truncal ataxia, hypotonia, late ambulation, and impaired cognition (Steinlin et al., 1998). With Cayman ataxia one characteristic is a marked cerebellar hypoplasia (Nystuen et

al., 1996). Joubert syndrome was characterized by aplasia or hypoplasia of the cerebellar vermis, absence of pyramidal decussation, and malformations in multiple brainstem structures. Thus, UTS, DES, Cayman ataxia, and Joubert syndrome, all share cerebellar hypoplasia, but with some variations depending upon the pathological condition. As a result, it is not reasonable to conclude that there are at least two syndromes with entirely similar MRI scans.

Among these four closely related syndromes, UTS, with two subgroups, appears to be a unique syndrome, with the main distinctive characteristic of habitual diagonal-sequence locomotion on all four extremities (quadrupedalism), which may emerge early or late in childhood, depending upon the existence of early hypotonia. Accordingly, UTS was classified into two subgroups: Type-I, early emergence of quadrupedalism without prior hypotonia, and Type-II, late emergence of quadrupedalism with early hypotonia, late improvement. By contrast, the individuals affected by DES, Cayman ataxia, and Joubert syndrome, all exhibited early hypotonia, with late ambulation or no ambulation at all, with or without assistance. Genetically, UTS also differs from others, being associated with different genetic mutations, and exhibiting genetic heterogeneity. This is indeed a characteristic of many syndromes and diseases. Namely, "*genetic heterogeneity is a common property of virtually all human genetic diseases*" (Ozcelik et al., 2008b). Moreover, UTS is distinguished from closely related syndromes with normal stature and normal muscle tone, in Type-I cases even during early childhood, and in Type-II cases after late childhood. For these reasons, UTS may be considered as a distinct entity among cerebellar ataxias.

3. Locomotion

The most impressive characteristic of Uner Tan syndrome is the habitual locomotion on all four extremities, with diagonal-sequence quadrupedalism (first suggested in Tan, 2005d). The other form of quadrupedal locomotion—lateral sequence gait—is a characteristic walking sequence for most non-primate species, with a hind limb touching down followed by an ipsilateral forelimb touchdown. By contrast, most primates walk on all four extremities using diagonal-sequence quadrupedal locomotion, where hind limb touchdowns are followed by contralateral forelimb touchdowns (Muybridge, 1887; Hildebrand, 1967; Prost, 1969; Rose, 1973; Rollinson & Martin, 1981; Meldrum, 1991; Schmitt & Lemelin, 2002). Fig. 3 illustrates diagonal sequence quadrupedal locomotion in a tetrapod (top) and a non-human primate (bottom), and also shows ground reaction forces (arrows) on the ipsilateral and contralateral forelimbs and hind limbs.

Although most primates use the diagonal-sequence gait for their preferred locomotion, it is, however, not without cost. Namely, the diagonal-sequence gait the hind limb touchdowns fall together with ipsilateral forelimb touchdowns, which may cause interference between the ipsilateral hind limbs and forelimbs (Hildebrand, 1968; Larson & Stern, 1987). Despite this constraint, most primates habitually walk on all four extremities using this type of locomotion, which implies there may be an evolutionary advantage of the diagonal sequence gait with regard to manual skills and brain development, since only these primates are associated with the hominoid evolution favoring the emergence of human beings with an enlarged brain, most complex neural circuits, high cognitive abilities, including language, and highly developed hand skills. The non-primate mammals using lateral-sequence quadrupedal locomotion did not show a similar phylogenetic progress compared to those with diagonal sequence quadrupedal locomotion.

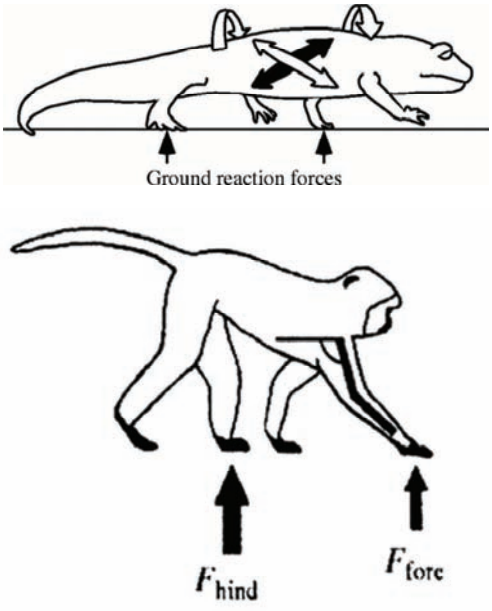

Fig. 3. Examples of diagonal sequence footfall patterns in a tetrapod and a non-human primate, also showing the ground reaction forces (arrows) on the ipsilateral and contralateral forelimbs and hind limbs. Notice greater ground reaction forces on the left forelimb and the contralateral right hind limb during walking on all four extremities in a tetrapod, and greater vertical force on the left hind foot (F_{hind}) than the contralateral (right) fore foot (F_{fore}) during diagonal sequence quadrupedal locomotion in a non-human primate (modified from Schmitt, 2003).

With regard to the origins of the diagonal sequence quadrupedal gait, most authors accentuated the importance of maintaining balance on the small-sized terminal branches of trees, i.e., the importance of habitually arboreal living (Cartmill et al., 2002; Demes et al., 1994; Hildebrand, 1967; Lemelin et al., 2003; Prost & Sussman, 1969). However, no environmental mechanisms could be revealed to explain this particular footfall pattern in primates (Stevens, 2008; Cartmill et al., 2002; Shapiro & Raichlen, 2005; Stevens, 2003, 2008). So, the question about the evolutionary mechanisms of the primate quadrupedal locomotion remained unresolved, at least concerning its benefits for balancing on the fine terminal branch settings, as Shapiro and Raichlen (2006) stated that there was "*no consensus on why primates prefer this unusual type of gait.*" However, a more satisfactory solution could be found in this context if the evolutionary origins of the quadrupedal locomotion were to be deeply examined, considering the whole spectrum of evolution, not only the primates, because the neural circuits for the diagonal-sequence quadrupedal locomotion existed even in the most primitive animals, including those during the transition from water to land. Namely, this type of locomotion is indeed phylogenetically the oldest locomotor trait of tetrapods (four-legged animals). Fossils 395 million years old were recently discovered on the Polish coast (Niedzwiedzki et al., 2010). From the fossil tracks left by a tetrapod animal it was concluded that this animal walked with diagonal strides, reflecting lumbering locomotor movements similar to their fishy ancestors living in marine environments (Fig. 4).

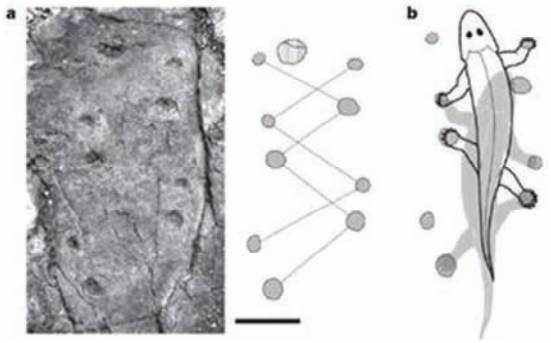

Fig. 4. Trackways. **a:** Muz. PGI 1728.II.16. (Geographical Museum of the Polish Geological Institute). The trackway shows hand and foot shapes in a diagonal stride pattern; **b:** a generic Devonian tetrapod fitted to the trackway. Notice the lumbering diagonal sequence quadrupedal locomotion of this tetrapod, similar to its ancestral forms living in water.

Interestingly, the quintessence of this kind of locomotion did not change during evolution, through salamanders and tuataras (Reilly et al., 2006), to the emergence of non-human primates and even human beings exhibiting diagonal movements between arms and legs during upright walking (Donker et al., 2001). Fig. 5 illustrates three contemporary, healthy human beings exhibiting diagonal-sequence arm-leg movements during their natural upright walk (above) and—requested—quadrupedal locomotion (below).

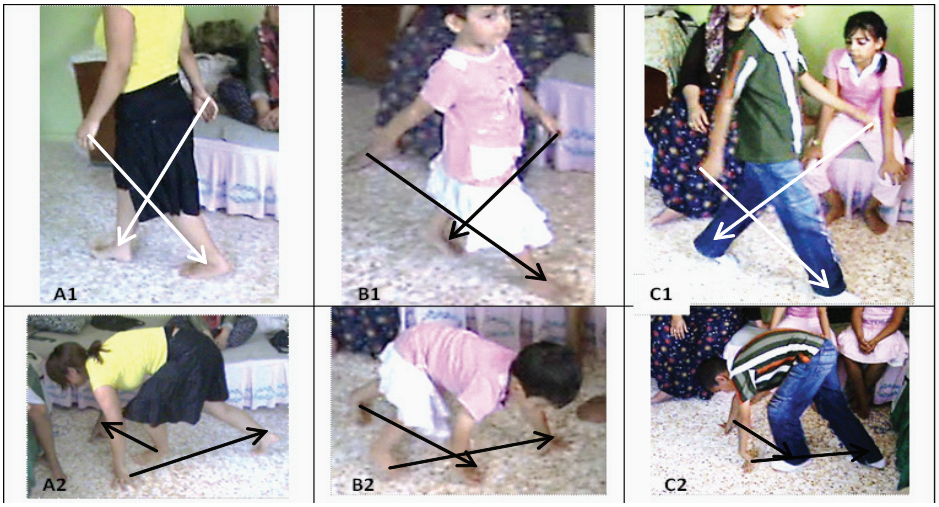

Fig. 5. Diagonal-sequence arm-leg movements (left hand-right foot *vs* right hand-left foot) during walking on two legs (above, bipedal gait) and walking on all four extremities (below, quadrupedal gait) in normal individuals. A1, A2: girl 17 YA; B1, B2: girl 4 YA; C1, C2: boy 14 YA. Photographs are courtesy of Derya Deniz Elalmış (post-doc fellow).

This phylogenetic analysis suggests that the neural circuits for the diagonal-sequence quadrupedal locomotion have been preserved for nearly 400 million years, beginning with

the ancestors of the first tetrapods even before transition from water to land, to the emergence of the non-human and human primates. Consequently, a consideration of the mechanisms of the inheritance of neural circuits responsible for the diagonal-sequence quadrupedal locomotion or even the diagonal sequence lumbering locomotion—prior to tetrapods—would be enlightening for the origins of the diagonal-sequence quadrupedal locomotion in non-human primates and human beings. Fig. 6 illustrates ancestral examples of diagonal sequence lumbering locomotion in tetrapods from the Devonian period (A, B), and essentially similar lumbering diagonal-sequence quadrupedal crawling locomotion in a modern human child (C, D). The animal depicted in Fig. 6B is one of the earliest tetrapods, called Acanthostega, a half-fish, half-reptile with legs and feet rather than fins, that inhabited a swamp, approximately 360 MYA (Clack, 2011). Notice the essential similarities between the locomotion of the earliest tetrapods and that of a modern child, circa 360 million years later, apparently due to the conservation of the ancestral neural networks within the spinal cords of these very primitive and most modern species.

Fig. 6. Diagonal-sequence quadrupedal locomotions (see arrows) with lumbering in a generic Devonian tetrapod during the time of transition from water to land (A), proposed picture of *Acanthostego,* one the most primitive tetrapods with lumbering diagonal-sequence quadrupedal locomotion, a half-fish, half-reptile that lived in a swamp, 360 MYA (B); a modern human child crawling on all fours with accompanying lumbering movements (C, D).

Consistent with these considerations, the scientific literature suggested that the neural networks responsible for diagonal sequence quadrupedal locomotion have been preserved for at least 395 million years since the Devonian tetrapod-like fishes (Daeschler, et al., 2006; Shubin, et al., 2006; Niedzwiedzki et al., 2010). In this context, Castillo et al. (2009) reported an evolutionarily conserved, daldh2 intronic enhancer in the frog, mouse, and chicken, being also

involved in the formation of the neural tube throughout the vertebrate species. Interestingly, this evolutionary conservation of the main enzyme for shaping the neural tube is essentially related to the evolutionary conservation of the neural networks for the diagonal-sequence quadrupedal locomotion. According to these authors, raldh2 expression plays an indirect role in the development of the spinocerebellar proprioception, dorsal spinal cord pathways, and spinal cord proprioception. Therefore it is not surprising that the spinal neural networks for the diagonal-sequence quadrupedal locomotion may also have been conserved for the last 100 million years during phylogeny. In this context, Whiting et al. (2003) reported the re-evolution of wings in wingless stick insects and concluded that "*wing developmental pathways are conserved in wingless phasmids.*" Accordingly, Castillo et al. (2009) argued "*thus it is feasible to search for core, conserved vertebrate developmental gene regulatory networks that can be used, in selected cases, to infer how specific vertebrate adaptations have emerged…*"

The mechanisms of this evolutionary preservation of the basic neural networks responsible for diagonal sequence quadrupedal gait remain, however, unresolved. Genetics of the evolutionary development would probably shed some light on this subject.

Figs. 7-9 illustrate this kind of ancestral gait in human beings with Uner Tan syndrome. Notice the walking patterns in each case with coincidence (interference) of the contralateral limbs and feet in the Iskenderun family (Fig. 7), especially on the left sides of the individuals depicted in the right column. The cases from the Adana family also exhibited interference of the left hands and feet during diagonal-sequence quadrupedal locomotion (Fig. 8). The alternate interferences between the ipsilateral hands and feet during quadrupedal locomotion were also remarkable in the quadruped man from the Kars family (Fig. 9).

Fig. 10 shows examples of the typical upright standing postures of the cases, inclined forward with flexed knees and trunk. Their upright standing postures could best be described as "the flexor-dominant posture," similar to non-human primates, which also exhibit flexed knees and trunk during upright standing (Preuschoft, 2004).

Fig. 7. Cases with Uner Tan syndrome from the Iskenderun family, exhibiting diagonal sequence quadrupedalism. Notice the interferences of the ipsilateral hand and feet due to diagonal locomotion.

Fig. 8. Cases from Adana with Uner Tan syndrome, exhibiting habitual diagonal sequence quadrupedal locomotion. Notice the fist walking visible in the left hands, bent fingers of the right hands, and the interferences of the left hands and feet due to diagonal quadrupedalism.

Fig. 9. A case from Kars with Uner Tan syndrome exhibiting diagonal sequence quadrupedalism. Notice the hand shoes and the interference of the right hand and right foot (left), and left hand and left foot (right) due to diagonal quadrupedalism.

Interestingly, in one case from Adana (Fig. 10, left), the brachial index (arm to leg ratio: radius as % of humerus) was found to be 90%, and 83% in a man who walked quadrupedally at a young age, but who was biped-ataxic in middle age (Tan, 2006c). The brachial indexes in Pan paniscus (Bonobo), A. afarensis (Lucy), H. habilis, and Homo sapiens were found to be 91.9, 90.7, 79.5-93.2, and 79.6, respectively (Groves, 1999). So the ratio of 90% for the quadruped man shown on the left of Fig.10 was similar to the ratios in Bonobos, A. afarensis (Lucy), and H. habilis. On the other hand, the cases walking on all four extremities with bent fingers and even fists shown in Fig. 11 may reflect the knuckle-walking trait in our ancestors (Richmond & Strait, 2000).

Fig. 10. Upright standing postures of cases with Uner Tan syndrome from Adana (left) and Iskenderun (middle and right). The man (middle) was the only case who could not stand up without assistance. He was also the only case with an arm to leg ratio of nearly one. Notice the flexor dominant upright postures (bent forward) similar to other cases exhibiting Uner Tan syndrome.

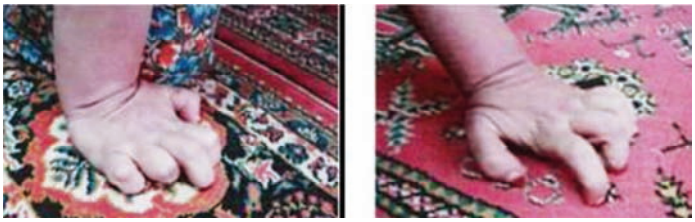

Fig. 11. The postures of hands of a case from the Adana2 family during walking on all four extremities. Notice that bent fingers have been observed in some cases with the syndrome instead of the palm-walking seen in most cases.

4. Forelimb and hind limb weight supports

Non-primate quadrupedal mammals usually support their body weight more on the forelimbs than their hind limbs (Demes et al., 1994; Schmitt & Lemelin, 2002). By contrast most primates support their body weight more on their hind limbs than their forelimbs during diagonal sequence quadrupedal locomotion, whether they are standing or moving, on the ground or in trees (Kimura et al., 1979; Demes et al., 1994; Schmitt, 2003; Schmitt & Hanna, 2004). The increased hind limb weight support in non-human primates is generally interpreted as an adaptation that reduces stress on the forelimb joints, facilitating the forelimb mobility, especially for arboreal locomotion (Reynolds, 1985; Larson, 1998). Despite its evolutionary importance, the mechanism used by primates to achieve this important kinetic pattern remains unclear. Raichlen et al. (2008) suggested that the pattern of primate weight support may have evolved as a byproduct of other traits. The role of the body mass

distribution in primate weight support was also excluded: "*body mass distribution is unlikely to be the sole determinant of footfall pattern in primates and other mammals.*" (Young et al., 2007). We found similar body mass distributions on the footfall patterns in human quadrupeds, i.e., less support on their hands (24% of their body weight) than their feet (76.0%). These results are consistent with non-human primates. For example, spider monkeys support less than 30% of their body weight on their forelimbs, and capuchins about 40% (Kimura et al., 1979; Kimura 1985; Reynolds 1985; Schmitt, 1994; Wallace & Demes, 2008). Reynolds (2005) reported 30-45% of the body weight was exerted on the forelimbs during locomotion of eight primates. The human quadrupeds also support their body weight more on their hind limbs than their forelimbs, like most of the primates. This body weight support pattern on hands and feet in human quadrupeds is consistent with the hypothesis that less body weight on the hands than on the feet would be beneficial for fine manual motor skills in primates. Complete freeing of hands due to upright walking in human beings would be entirely associated with highly developed hand skills compared to the non-human primates walking on all four extremities.

5. Darwinian medicine

"*…why our bodies are vulnerable to certain kinds of failure*" (Nesse et al., 2006). The question may be asked for our cases: why are only some rare cases predisposed to walk on all four extremities? The quest to find an answer to the first question was the starting point for establishing a new discipline, "*Darwinian medicine,*" which is a novel concept providing a foundation for all medicine (Zampieri, 2009). Fig. 12 illustrates the pyramidal structure of Darwinian medicine, with evolutionary biology at the top influencing anthropological, genetic, and microbiological perspectives.

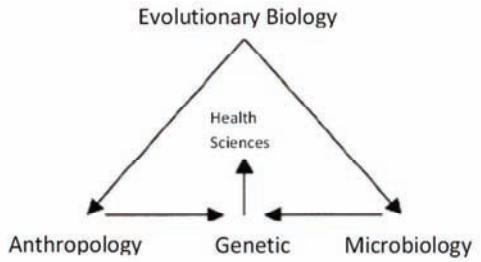

Fig. 12. Theoretical structure of Darwinian medicine. From Zampieri (2009), with permission.

"*Contemporary Darwinian medicine is a still-expanding new discipline whose principal aim is to arrive at an evolutionary understanding of aspects of the body that leave it vulnerable to disease… It tries to find evolutionary explanations for shared characteristics that leave all people vulnerable to a disease.*" (Zampieri, 2009). The application of evolution by natural selection to medicine, i.e., "evolutionary or Darwinian medicine," may be useful to help us understand better why diseases exist despite natural selection (William & Nesse, 1991; Nesse & Williams, 1994; Stearns, 1998). In this context, a number of diseases were considered as Darwinian disorders, suggesting that "*Darwinian medicine allows us to see the body as a product of natural selection, full of trade-offs and vulnerabilities that all too often lead to disease*" (Nesse, 2001) such as

tuberculosis, Huntington's disease, and depression (Eskenazi, et al., 2007) in addition to conditions such as obesity, anxiety, pain, nausea, cough, fever, vomiting, fatigue, epilepsy (Scorza, et al. 2009), obsessive compulsive disorder (Abed & Pauw, 1998), and other psychiatric disorders including schizophrenia (Pearlson & Folley, 2008). In this context, Uner Tan syndrome may also be considered as a further example of a Darwinian disease.

Under Darwinian diseases, Rapoport (1988) first considered Alzheimer's disease as a "phylogenic regression" under the main heading "*phylogenic diseases,*" "*that compares brain aging involution to the reversed phenomenon of Darwinian evolution*" (Ghika, 2008). Similarly, many neurodegenerative diseases such as Parkinson's disease (Vernier et al., 2004), gait disorders (Tan, 2005d; Tan, 2006a, b; Tan, 2010a), schizophrenia (Brüne, 2004; Burns, J.K. (2004), and the highest level gait disorders including Uner Tan syndrome, with its simian-like gait and posture or apraxia, i.e., the re-emergence of old automatism of pre-human gait, may also be considered under these phylogenic diseases (Ghika, 2008). In this context, the paleoneurologic standpoint recently introduced to clinical neurology may help us to more deeply understand the pathogenesis of the neural disorders, provided that they are re-considered under evolutionary principles.

6. Non-human primates

The most prominent feature shared by all of the cases exhibiting Uner Tan syndrome and all non-human primates was the diagonal sequence quadrupedal locomotion. One of the cases (1/25) (the man in the Iskenderun family) did not have an opposable thumb, unlike healthy human beings. All apes (chimps, bonobos, gorillas, orangutans, gibbons) have opposable thumbs, but New World monkeys (monkeys of South and Central America) do not have opposable thumbs.

Although the Uner Tan syndrome cases usually had dysarthric speech, some of them (15/22, 68.2%) could not speak a single word, but rather expressed themselves with one or two simple sounds, as do non-human primates.

Interestingly, in one man from Adana (on left of Fig. 10), the brachial index (arm to leg ratio: radius as % of humerus) was found to be 90%, and 83.0% in a quadruped man with transition to a bipedal ataxic man during middle age (Tan, 2006, c). The Childs' quadruped man discovered in Turkey nearly a hundred years ago also had a relatively high 92.0% arm to leg ratio. These arm to leg ratios are more or less similar to non-human primates. Namely, the brachial indexes in Pan paniscus (Bonobo), A. afarensis (Lucy), H. habilis, and Homo sapiens were found to be 91.9, 90.7, 795-93.2, 79.6±2.5, respectively (Groves, 1999). So the 90% ratio for the quadruped man shown on the left of Fig. 10 was similar to the ratio in the Bonobo, A. afarensis (Lucy's), and H. habilis. On the other hand, the cases (see Fig. 11) walking on all four extremities with bent fingers and even fists may reflect the knuckle-walking trait in our ancestors (Richmond & Strait, 2000). Moreover, some cases exhibited heavy supraorbital tori similar to our early ancestors (see Figs. 13-14).

6.1 Supraorbital torus

The supraorbital torus, also called the supraorbital ridge, brow ridge, supraorbital arc, arcus superciliaris, or supraorbital margin, is a bony ridge located just above the eye socket. The

torus is massive in gorillas and chimpanzees and was also well developed in extinct hominids. It is more prominent in males than females (from the Encyclopedia Britannica). It was first described by Richard Owen in 1855 as a distinctive difference between chimpanzee and human skulls, suggesting that the possession of the supraorbital torus was the unique structural difference between the ape and human crania, being unaffected by diet, habit or muscular exertion (Owen, 1885, p.39): "*The prominent supraorbital ridge… is not the consequence or concomitant of muscular development; there are no muscles attached to it that could have excited its growth… We have no grounds, from observation or experiment, to believe the absence or the presence of a prominent supraorbital ridge to be a modifiable character, or one to be gained or lost through the operations of external causes inducing particular habits through successive generations of species. It may be concluded, therefore, that such feeble indication of the supraorbital ridge, aided by the expansion of the frontal sinuses, as exists in man, is as much a specific peculiarity of the human skull… as the exaggeration of this ridge is characteristic of the chimpanzee.*" According to Owen, "*the supraorbital torus was an unmodifiable, nonfunctional, nonadaptive, definitely simian trait.*" (Russell (1985).

Fig. 13 shows the MRI pictures of the skulls taken from a monkey (left) and a modern man (right), as examples of the supraorbital tori (arrows) in non-human and human primates.

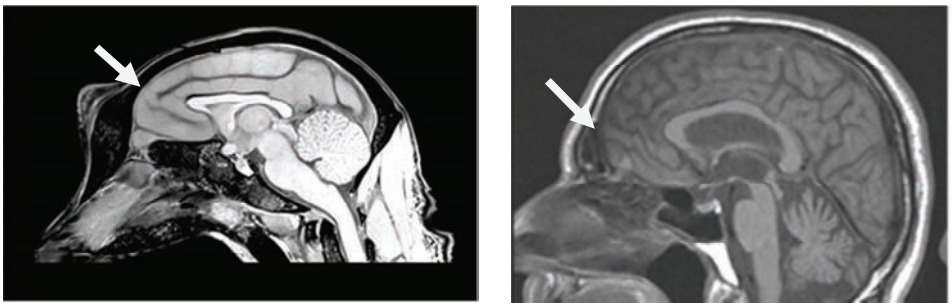

Fig. 13. MRI pictures with supraorbital tori (arrows) in a 6-year-old, female rhesus monkey (left) and a 75-year-old modern man (right, one of the authors, UT). Monkey MRI from Tammer et al. (2009), with permission. Notice the significantly heavier supraorbital torus in monkey than man.

The supraorbital torus or ridge, as a most prominent craniofacial structure, may be one of the most significant differential traits to define the species of hominids. "*The recent human fossil record has a confusing pattern of variation, with numerous vaguely defined taxa (e.g., 'archaic' H. sapiens, 'modern' H.sapiens, Homo heidelbergensis, Homo helmei, Homo rhodesiensis), most of which are not widely accepted… A major source of this confusion is the lack of established unique derived features of 'anatomically modern' H. sapiens.*" (Lieberman et al., 2002). In the context of primate evolution the function of these brow ridges and their developmental origins are relevant to the evolution of primates including human beings. Accordingly, the size of these tori shows variations in different species of living and fossil primates, being negligible in modern humans but relatively pronounced in, for instance, fossil hominids, and apes such as chimpanzees and gorillas, and being slightly prominent in gibbons and orangutans, well-developed in baboons, moderately developed in macaques, but poorly developed in vervets (Russell, 1985).

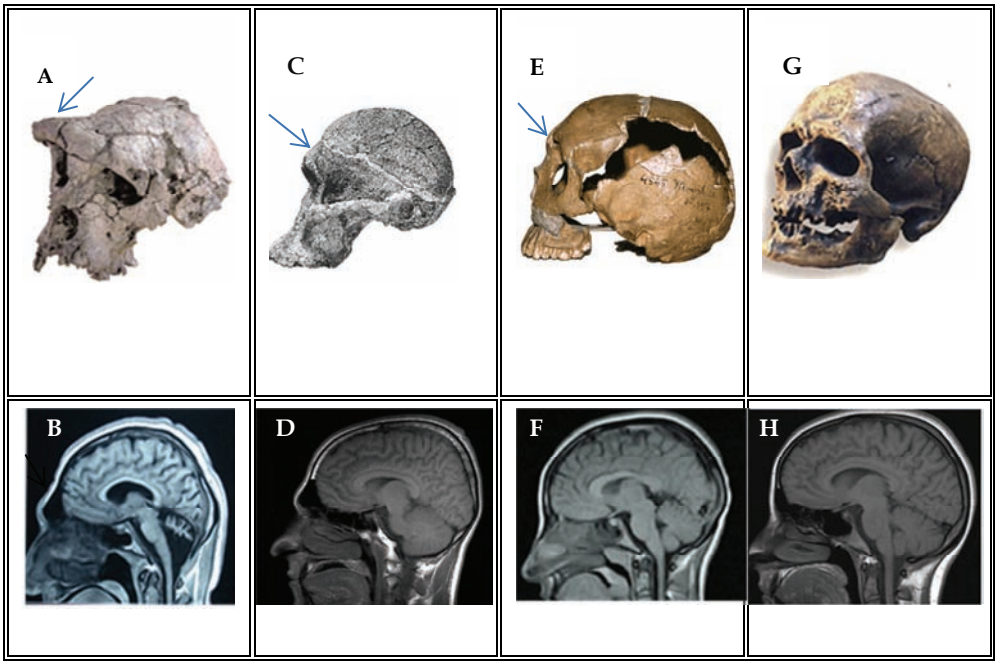

Fig. 14. Supraorbital tori in hominids, modern quadruped humans, and modern biped humans. A: Sahelanthropus tchadensis, 6 to 7 MYA, with heavy supraorbital tori; B: MRI skull of a modern quadruped man (Iskenderun family), with prominent supraorbital torus; C: Homo habilis, about 1.8 MYA, with heavy supraorbital ridges; D: MRI skull of a modern quadruped man with protruded supraorbital ridges (Diyarbakir family); E: Skull of homo sapiens neanderthalensis, no supraorbital ridges. F: skull of a modern normal individual with no supraorbital ridges (a sibling from the Iskenderun family); G: skull of homo sapiens sapiens (Cro-Magnon man), lived in Europe between 35.000 and 10.000 YA and virtually identical to modern man, with nearly no prominent supraorbital ridges.

Fig. 14 illustrates the supraorbital tori (arrows) in Sahelanthropus tchadensis (A), nicknamed "Toumai," discovered in Chad, Central Africa, the oldest known hominid or near-hominid species, with a small brain of approximately 350 cc, and protruded supraorbital tori (Brunet et al., 2002; Wood, 2002). There is no consensus about the type of locomotion (bipedal or quadrupedal). The species probably emerged around the time when the hominids diverged from chimpanzees, 6-7 MYA, and exhibits characters close to our common ancestor (Wood, 2002). Fig. 14B illustrates the cranial MRI from a modern quadruped man, one of the cases in the Iskenderun family, and exhibits a prominent supraorbital torus. Fig. 14C shows the skull of Australopithecus Africanus, first discovered in 1924 (Dart, 1925), with prominent supraorbital torus and a relatively larger brain (480-520 cc) when compared to chimpanzees, and an estimated age of 3 to 2 MYA. Fig. 14D shows the skull MRI of a modern quadruped man from the Diyarbakir family, with a prominent supraorbital torus. Fig. 14E shows a skull of homo sapiens neanderthalensis discovered near Krapina in Croatia, who lived between 42.000-32.000 YA (notice the decrease in the supraorbital torus compared to the much older skulls depicted in A and C). Fig. 14F is a

skull MRI from a modern man with no visible supraorbital tori. The skull presented in Fig. 14G is an example of "homo sapiens sapiens" (Cro-Magnon man), who lived in Europe between 35.000 and 10.000 YA, and which is virtually identical to modern man, with very slightly prominent supraorbital ridges. Cro-Magnon man was characterized by well-developed hand skills for fine arts, tool making, hunting, and drawing, and represented the first early modern humans, with an average brain capacity of 1600 cc (Goudot, 2002). Fig. 14H shows the MRI skull of a modern man, which shows no supraorbital tori.

The significance and origin of the supraorbital tori in hominids remains unknown in physical anthropology. With regard to the much discussed effect of mastication on the occurrence of this structure, Kupczik et al. (2009) argued that "*our data support the notion that the growth of the supraorbital torus region is not a result of a high-strain loading regime and morphology in adult fossil hominins is unrelated to mastication.*" On the other hand, Fiscella and Smith (2006) reported in this context: "*Understanding the function of brow ridge variation in living and fossil human populations is relevant to questions of human evolution. Results agree with previous research supporting the existence of special influences between the neural and orbital-upper facial regions on brow ridge length during ontogeny.*"

7. Atavism (reverse evolution)

Held (2009) stated in his book, Quirks of Human Anatomy, "*how much neural rewiring was needed to convert a quadrupedal simian to a bipedal hominin? Maybe not much: (1) a single mutation in an axon-guidance gene can make a mouse hop like a rabbit (cf. kangaroo rats), and (2) a human syndrome (due to one allele?) was found in Turkey where affected adults revert to walking on all fours [Tan 2006]! Can evolution rewire locomotion faster than arousal cues?*" Ghika (2008) stated in his article: "*In a way, a demented patient with language dysfunction returns to the level of thinking and communication of an early primate, like the Uner Tan syndrome walks like a primate quadruped with curved fingers during wrist walking with arm and leg ratios of human-like apes and possess primitive language and mental abilities.*" Therefore the quadrupedalism was proposed to be a phenotypic example of evolution in reverse (see Tan, 2010a), i.e., "*the reacquisition of the same character states as those of ancestor populations by derived populations*" *(Teotonio & Rose, 2001). On the other hand, Tan (2010a) also suggested that "UTS may be considered within the framework of phylogenetic diseases associated with phylogenetic regression (Bailey, 1978), and this may in turn be related to the theory of human backward evolution.*"

The ancestral characteristics of the UTS cases, such as habitual quadrupedal locomotion, no speech but one or two sounds, very limited vocabulary in dysarthric cases with no conscious experience, standing with bent knees and trunk (flexor posture contrary to extensor posture in modern humans), and heavy supraorbital tori, fist walking with bent fingers, and non-opposable thumb observed in some cases, may be associated with atavism or reverse evolution, which, in turn, were considered under Darwinian or phylogenic diseases (see above). Atavism, or evolutionary throwback, was defined as "*the reappearance of a 'lost character' (either morphological or behavioral) that was typical of remote ancestors*" (Tomic & Meyer-Rochow, 2011). This definition is relevant to human quadrupedalism, which is not only one of the main symptoms of UTS, but it can also be observed in individuals with entirely normal brains (Tan, 2007a; Tan & Tan, 2009). Accordingly, the cases with the novel syndrome were first reported as live cases for backward evolution in human beings (Tan, 2005d; Tan, 2006a, b, c). This may be associated with mutation in a single gene: "*Unertan Syndrome suggests that the erect posture of our ancestors may have occurred by a punctuated evolution, as a result of a mutation in a single gene or*

in a gene pool" (Tan, 2005d). And, *"The genetic nature of this syndrome suggests a backward stage in human evolution, which is most probably caused by a genetic mutation"* (Tan, 2006a). Consistent with this hypothesis, single gene mutations were recently identified in single families: VLDLR in the Antep and Canakkale families (Ozcelik et al., 2008a), CA8 in the Iraqi family (Türkmen et al., 2009, WDR81 in the Iskenderun family (Gulsuner et al., 2011). These single genes were associated with the synthesis of proteins responsible for the structural and functional organization of the brain, including the cerebellum, which controls locomotor coordination and especially truncal balance. It was proposed that these mutations were most likely associated with the emergence of the quadrupedal locomotion in humans. However, no single gene has hitherto been identified that was directly responsible for the emergence of human quadrupedalism as an atavistic feature.

The concept of backward evolution, or reverse evolution, or atavism, caused an interesting debate among scientists, asking if evolution may be reversible or not. In fact, probably due to incomplete definitions, reverse evolution has nothing to do with the direction of evolution, which may not have a direction due to randomness in its origins. Evolution in reverse as another variation of evolution may easily be accounted for if the Darwinian medicine of phylogenetic diseases is taken into consideration instead of using the misleading terms for reverse evolution. Among these, atavism would better describe the situation. Studying the mechanisms of atavism as a reappearance of ancestral features would be more reasonable than struggling around phylogenetic ideas. Whatever may be, the theory of reverse evolution was seriously taken into consideration by many notable laboratories. For instance, Bridgham et al. (2009) recently found that resurrecting ancient proteins constrains the direction of receptor evolution, consistent with the notion of irreversibility of evolution. However, these authors did not report the behavioral correlates of the resurrected ancient proteins within their laboratory conditions. In this context, it must always be kept in mind that the atavism or reverse evolution both describe the behavioral or structural traits.

Consistent with the theory of reverse evolution, there are experimental studies suggesting it is plausible and testable (Teotonio & Rose, 2000, 2001, 2002), and there are indeed studies supporting the theory of evolution in reverse. For instance, Bekpen et al. (2009) reported a gene associated with Crohn's disease deleted about 50 MYA in primates could have been resurrected during human evolution. Harris et al. (2006) have succeeded in breeding a mutant strain of chicken with teeth, formerly only seen in their ancestors. This suggests modern chickens without teeth would still have ancestral genes available to be switched back on. Similarly, mutations in the Ubx gene produced four-winged flies, reflecting their ancestral species from more than 200 MYA (Lewis, 2006). Moreover, Tvrdik & Capecchi (2006) also demonstrated the reconstruction of a 530-million-year old gene in the modern mouse. Interestingly, VLDLR,, the gene associated with quadrupedalism in the affected cases of the Antep and Canakkale families, playing a role in neuroblast migration as a part of the reeling signaling pathway, is also conserved from stem amniotes (stem reptiles) to mammals (Bar et al., 2000) and even to avian species (Bujo et al., 1994), within a time span of about 350-400 MYA.

In addition to these examples for the process of reverse evolution, it was suggested some apes may have human ancestors, suggesting also backwards evolution (Filler, 2010). These results, however, contradict Dollo's Law (1893), which states that "*an organism is unable to return, even partially, to a previous stage already realized in the ranks of its ancestors.*" However, this law was not entirely supported by researchers after Dollo's time. Human

quadrupedalism for instance, is the most impressive contradictory example of this law. Accordingly, Siler and Brown (2011) stated that "*Dollo's law came into question recently with the advent of phylogenetic methods and new tools for ancestral character state reconstruction… The results of our study join a nascent body of literature showing strong statistical support for character loss, followed by evolutionarily reacquisition of complex structures…"*

Actually, atavism was first demonstrated more than a hundred years ago by Castle (1906; cited by Wright, 1978) who succeeded in obtaining guinea-pigs with well-developed little toes after selective breeding these animals, which normally have three toes. This phenomenon was later explained as "*atavistic polydactyly"* (Wright, 1978). Tomic and Meyer-Rochow (2011) provided more convincing examples for the atavistic features in their review article about atavism, such as whales with rudimentary hind limbs (Hall, 1984), coccygeal projections as truly atavistic human tails (Dubrow et al., 1988), a mutant mouse without tail formation due to down-regulated signaling in the Wnt-3a gene (Chan et al., 2002). These are structural throwbacks, in contrast to human quadrupedalism, which is an example of a functional throwback, which may also be defined as "*evolution in reverse character."* These apparently violate Dollo's law, and, since 1893—Dollo's time—there have been numerous studies demonstrating violations of this law (Galis et al., 2010; Wiens., 2011), such as Wiens (2011), who reported the re-evolution of mandibular teeth lost 230 MYA in the frog *Gastrotheca,* which reappeared in the last 5-17 million years. Moreover, the lost wings in stick insects were re-evolved, suggesting that "*living developmental pathways are conserved in wingless phasmids"* (Whiting et al., 2003); lost digits were re-evolved in lizards (Galis et al., 2010), etc. These studies, concerning the process of re-evolution, are consistent with the concept of evolution in reverse, both involving the conserved patterns of the ancestral characters or structures acquired millions of years ago, and emerging much later during the developmental constraints.

8. Complex systems and self-organization

A dictionary definition of the word "complex" is: "*consisting of interconnected or interwoven parts"* (Bar-Yam, 1997, p. 1). Examples for complex systems are governments, families, the human body in its physiological perspective, an individual in psychological perspective, the brain, weather, the ecosystem of the world, and sub-world ecosystems such as desert, rainforest, ocean, etc. The complex systems involve parts, which are interconnected or interwoven, contrary to simple systems. Single independent disciplines diverge as specific knowledge increases in simple systems, but the behavior of the parts must be considered as a whole consisting of converging disciplines with interacting elements creating the behavior of the whole.

Many complex systems in physics have the tendency to spontaneously generate novel and organized forms, such as ice crystals, galactic spirals, cloud formations, or lightning flashes in the sky, or polygonal impressions in the earth. Fig. 15 illustrates self-organized landscapes in Turkey: on the left, terraces, travertines in Pamukkale (cotton castle) spontaneously made of carbonate minerals left by the flowing warm water. The other pictures are "fairy chimneys" rock formations in Cappadocia, which were also spontaneously formed through volcanic activity (some three million years ago), wind, water, and temperature fluctuations. Residents believed the region was inhabited by fairies. These formations are in no way designed by anyone or anything, not even by natural

selection, being entirely the art of nature with self-organizing properties within dynamical complex systems, following the principle: "*the sum of the parts is greater than the parts taken independently,*" contrary to Sir Isaac Newton who argued: "*the motion of the whole is the sum of the motion of all the parts.*"

Fig. 15. Examples of self-organized nature: left and center, travertines, terraces spontaneously made of carbonate minerals left by the flowing warm water in Pamukkale ("cotton castle"), Turkey: right, "Fairy Chimneys" (roof-like formations) in Cappadocia, Turkey, spontaneously formed from the solidified lava streams, ash, and tuff stone, through rain, wind, and temperature fluctuations.

The above exemplified natural complex systems, with a strong tendency to self-organize, may also be applied to biological systems. For instance, insects can spontaneously build nests or hives, hunt in groups, and explore the food resources of their environment (Camazine et al., 2002), like the formation of the colored patterns of many creatures such as butterflies, zebras, jaguars, etc (Ball, 2001). The self-organization, *i.e.*, "*the spontaneous formation of patterns and pattern change in open nonequilibrium systems*" (Kelso, 1995, preface), is essentially the quintessence of all living systems. The evolution of the biological forms and structures may also be associated with self-organization. In this context, some authors have questioned the centrality of natural selection in evolution, since Darwinism essentially ignores the principles of self-organization. Accordingly, Waldrop (1990) suggested:

"Complex dynamic systems can sometimes go spontaneously from randomness to order; it is a driving force in evolution? Have we missed something about evolution – some key principle that has shaped the development of life in ways quite different from natural selection, genetic drift, and all the other mechanisms biologists have evoked over years?... Yes! And the missing element… is spontaneous self-organization: the tendency of complex dynamical systems to fall into an ordered state without any selection process whatsoever."

Oudeyer (2006, p.1) also suggested:

"Thus, the explanation of the origins of forms and structures in the living can not only rely on the principle of natural selection, which should be complemented by the understanding of physical mechanisms of form generation in which self-organization plays a central role."

The process of self-organization is closely coupled with "emergence," a fundamental property of complex systems: *"a new property or behavior, which appears due to non-linear interactions within the system; emergence may be considered the product or by-product of the system… It is the product of interconnections and the interaction makes it dynamic and unpredictable; entities, interactions, their environment and time are key contributors to emergence, even though there is no simple relationship between them"* (Dobrescu & Purcarea, 2011).

As mentioned above, different genes are found associated with a clinical condition. For UTS, we already know three genes which may be associated with the human quadrupedalism. However, considering the dynamical system theory, and the principles of self-organization, no genetic or neural code may be the causative factor for the human quadrupedalism. There are also rarely occurring cases of patients who had childhood poliomyelitis, and who have normal brains, speech, intelligence etc., and who also prefer walking on all four extremities, rejecting all measures to assist them to walk upright, such as using crutches. The first case noted of walking on all fours following childhood poliomyelitis was photographed by Eadweard Muybridge (1887, 1901), with photographs taken in rapid succession to create a movie using his zoopraxiscope (see Fig. 16). Despite his paralyzed leg the boy exhibited diagonal-sequence quadrupedal locomotion.

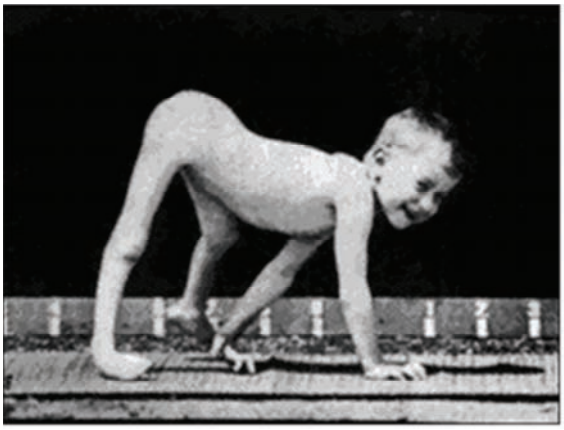

Fig. 16. Child with a paralyzed leg walking on all fours (Muybridge, 1901). Notice the diagonal-sequence quadrupedal locomotion with interference between the left foot and left hand.

This kind of adaptation to locomotor constraints occurs as a polio sequel in only a few individuals among millions of cases, as an emergent property of a complex system consisting of the mind-brain-body triad in human beings (Tan, 2007b). Much later, an adult man with a paralyzed leg as a polio sequel was reported (Tan, 2007a), who had an entirely normal brain and cognition, but who preferred quadrupedal locomotion, even though his father forced him to walk upright using crutches. Interestingly, these cases used diagonal-sequence quadrupedal locomotion.

There are millions of individuals with paralyzed legs as a result of polio, but the walking patterns these few cases exhibited are extremely rare. This suggests that the creation of an extremely rarely occurring motor pattern would occur randomly without any influence of a previously established genetic or neural code. This hypothesis may also be reasonably applied to the UTS cases for the emergence of a well-developed, easily performed quadrupedalism (habitual walking on all four extremities). UTS is also a rarely occurring condition, suggesting randomly occurring events in the emergence of human quadrupedalism. As mentioned above, the unpredictable outcomes of a complex system are related to the principles of the self-organizing processes.

The emergence of unpredictable outcomes within a complex system such as the human body is closely related to neural networks in the brain exhibiting "*self-organized criticality*" (Tetzlaff et al., 2010), which may play a role in the developmental processes with emergent outcomes as exemplified above for the emergence of new locomotor patterns. Although the self -organization remains an enigma in many respects, "*it is realized that no discipline on its own will be able to solve the enigma*" (Skar, 2003). By definition, however, "*organization arises through the interaction of its components (endogenously) or by some environmental influence (exogenously). Self-organization is neither and the curious thing is that no external force can be identified as the organizer… self-organization seems to be characterized by the almost spontaneous creation of global or semi-global patterns developed from local interactions among independent and autonomous components or agents. Creation and patterns are two basic components of self-organization. Patterns are often visible and transient, while creation is less visible and mysterious. Creation of self-organization is, as a special case, believed to be triggered by 'strange attractors'*" (Skar, 2003). An attractor can be defined as a kind of steady state in a dynamical system, or, "*a set of states of a dynamical physical system toward which that system tends to evolve, regardless of the starting conditions of the system.*" There are three kinds of attractor: point attractor, periodic attractor, and strange attractor. "*A strange (or chaotic) attractor is an attractor for which the evolution through the set of possible physical states is nonperiodic (chaotic), resulting in an evolution through a set of states defining a fractal set. Most real physical systems (including the actual orbits of planets) involve strange attractors*" (http://science.yourdictionary.com/attractor. Fig. 17 shows different types of attractors. The brain itself has strange attractors, which are involved in each particular activity.

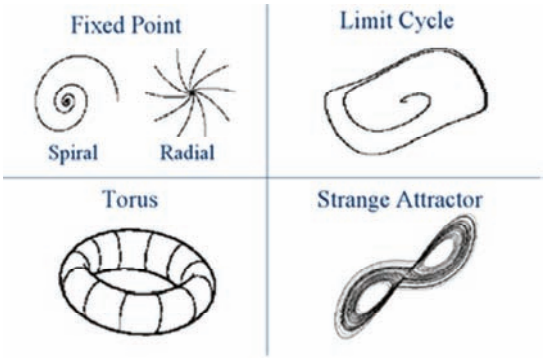

Fig. 17. Types of attractors.

For instance, the EEG plots showing the brain activity may exhibit one type of strange attractor while a person is at rest, but another type of strange attractor during, for instance, mathematical thinking. The unpredictability of consciousness may also be considered a strange attractor, or what we call "personality," as the consciousness itself is also a strange attractor. The brain, as a dynamic system with many strange attractors, may show state transitions, thereby creating novel and unpredictable patterns, such as during the postnatal development of children. For instance, various locomotion patterns or locomotor strange attractors may emerge during postnatal motor development in children and even in adult individuals. The common property of strange attractors is their unpredictability, which is one of the main constraints for the applicability of the physical concept of self-organization

to biological systems. However, new insights have been gained through increasing cooperation between biological sciences and computer modeling. For instance, bio-computational models of the primary visual cortex have revealed new and unpredictable lateral connectivities among neural networks emerging through input-driven self-organization (Skar, 2003). So there may be some inputs or common factors triggering the self-organizing process in a complex system. The common factor for individuals with UTS to trigger (input) a locomotor strange attractor, i.e., diagonal-sequence quadrupedal locomotion like the non-human primates, was their disability or difficulty in achieving upright walking. The rarely occurring locomotor pattern in UTS cases may be related to the unpredictability of the strange attractors.

An entirely different locomotor strange attractor emerged in a man from Tanzania, who exhibited all the symptoms of UTS, including no upright ambulation, quadrupedal locomotion, no speech, and impaired intelligence. However, an entirely new and unpredictable locomotor posture emerged in this man, as a strange attractor. Namely, the Tanzania man (Fig. 18) exhibited the same phenotype as UTS (Type-I) with truncal ataxia, inability to stand up and walk upright without assistance, mental retardation, no speech, no conscious experience, and walking on all four extremities, without early hypotonia. However, his quadrupedal locomotion was upside down, i.e., in face-up position. He used his hands and feet for locomotion, but used palms and heels instead of the soles. This is the first case reported in the scientific literature exhibiting UTS with quadrupedal locomotion but in reverse posture with face-up position.

Fig. 18. Tanzania man with UTS, walking on all fours but with inverse quadrupedal locomotion.

Fig. 19 illustrates further locomotor strange attractors in a paraplegic woman (left) and a man (right).

Both of them had had childhood poliomyelitis, and could not ambulate at all as a result. The woman always rejected crutches to help her to walk upright, but instead she spontaneously created an entirely novel walking style to ambulate around without assistance, by holding her ankles with her hands to travel forward and backward. The locomotion of the woman with a childhood polio sequel also occurs extremely rarely, there being one individual in Adana and another one in Istanbul, nearly 1000 km away from each other. The woman is now in her fifties, and she has managed using this type of locomotion since she was eight years old, after years of effort. The man in Fig. 19 also rejected crutches to help him to walk upright on two legs. Instead he developed another strange attractor: palm walking with jerking legs (palmigrade saltatoric locomotion).

Fig. 19. Examples of strange attractors: walking patterns of a paraplegic woman (left) and a man (right) both having emerged at about eight years of age, following childhood poliomyelitis.

The couple shown in Fig. 20 may also illustrate strange attractors. The father and mother were both paraplegic individuals due to childhood polio sequels, but when she was 10 years old the woman had learned to ambulate after long periods of exercise, and had learned to use palm walking with jerking legs with the help of her hip muscles, i.e., she exhibited saltatoric palm-walking. Her husband, despite having the same clinical picture, could not ambulate, but rather remained sitting without assistance. These two cases were also good examples of the emergence of strange attractors triggered by severe locomotor constraints.

As mentioned above, these adaptive self-organization phenomena may provide basic explanations for the emergence of the locomotor strange attractors, such as walking on all four extremities (face-down), inverse quadrupedalism (face-up), saltatoric palm-walking, and grasping-foot walking. In essence, the dynamical systems tend to control the outcome pattern of the system to find a compromise between "*which patterns can possibly be built from the systems components to begin with, and the structural constraints of the environmental situation*," and a synergetic pattern formation—with possible strange attractors—may be "intentional," with the self-organization phenomena being basic explanations for the adaptive behavior (Tschacher et al., 2003).

Fig. 20. Family with paraplegic mother and father. The mother was able to walk on her palms with jerking legs (saltatoric palm walking), but the father could not ambulate, despite having the same polio sequel as the mother

9. Central pattern generators; motor programs

A central pattern generator (CPG) for locomotion is a set of motoneurons responsible for creating a motor pattern (Grillner, 1985). Human quadrupedalism might be associated with CPGs, which are embedded in the spinal cord, spontaneously producing rhythmic locomotor activity (Hooper, 2000) without being controlled by the supraspinal centers above the brain stem (Hiebert et al., 2006). The spinal motor system seems to be similar in all quadrupeds and humans (Dietz, 2002). Individuals with or without UTS all use the same neural networks associated with diagonal-sequence quadrupedal locomotion as the non-human primates, probably because they all are using the common neuronal control mechanisms for locomotion (Shapiro & Jungers, 1994).

Until the discovery of CPGs, the dominant idea about the mechanisms of locomotion was based on the proprioceptive information and intact descending control from supraspinal centers, considering the results on spinal reflexes and the clinical observation of flaccid paralysis following spinal cord injury (Clarac, 2008). However, it was found in different laboratories that deafferented crayfish sometimes continued to produce spontaneous rhythmic bursts in motor axons innervating the leg muscles (Hughes & Wiersma, 1960). In accord with these findings, Wilson (1961) suggested *"it seems not too early to conclude that central oscillators in anthropods are of such fundamental importance that they are used even when other mechanisms might suffice."* These neural oscillators are characteristic of cyclic activities in many species. *"For locomotion, one usually refers to the term central pattern generator (CPG) to indicate a set of neurons responsible for creating a motor pattern. It should be emphasized indeed that 'pattern' is used here in a broad sense to indicate alternating activity in groups of flexors and extensors. Hence it is not implied that an overground walking animal would use the same pattern of muscle activation as the one seen."* (Duysens et al., 1998). These centrally generated spontaneous motoneuronal bursts, are, however, not the origin of normal locomotion in intact animals. Moreover, the CPGs do not reflect the coordinated walking pattern in intact animals, since it was shown that there are separate CPGs for each leg in the cat (Duysens et al., 1998). On the other hand, it was originally shown that spinalized cats with cut dorsal roots exhibited alternating contractions in ankle extensor and flexor muscles (Brown, 1911, 1912). The coordinated locomotor activity inducing quadrupedal locomotor movements was, however, produced by electrical stimulation of a specific region in the brainstem located below the intercollicular transection of decerebrate cats (the mesencephalic locomotor region) (Shik & Orlovsky, 1976). Depending on the stimulus strengths, the

electrical stimulation of this region induced different patterns of quadrupedal locomotion: walking, trotting, and galloping (Shik et al., 1966).

CPGs were also demonstrated in animals other than cats, including a wide variety of invertebrates and vertebrates (see Rossignol & Dubue, 1994, for a review).The presence of the CPGs in primates, including human beings, would be interesting, since the primate locomotion may not be related to the spontaneous or induced activity of the previously established spinal circuits because of the strong supraspinal control of the lower motor neurons. In accord with this, no stepping in hind limbs occurred in the macaque monkeys following spinalization (Eidelberg, 1981). This could be due to the increased role of the tractus corticospinals in primates, in suppressing the locomotor circuitry within the spinal cord by increased corticospinal control on the lower motoneuronal system for the relatively rough walking movements, and in facilitating skilled hand movements, especially in human beings.

In this context, Duysens et al. (1998) argued that, "*For Old World monkeys and higher primates the evidence is much less convincing.*" In humans, newborn infants may exhibit primitive step-like movements with external assistance (Forssberg, 1985). These stereotyped movements of newborns may be the basis for the adult locomotor patterns. The prenatal stepping movements were also considered to be further evidence for the hard-wired intraspinal circuits for locomotion. However, these prenatal and postnatal observations may not show the existence of the spontaneously active intraspinal CPGs in human beings. As Duysens et al. (1998) concluded: "*In contrast to the abundance of data in cats… there is relatively little known about spinal networks acting like CPGs in humans. The most convincing evidence for a CPG, i.e., fictive locomotion, has no direct equivalent in humans.*"

In light of the dynamical systems theory, the concept of CPGs formerly invoked much interest among motor neurophysiologists studying the origins of quadrupedal locomotion, but did not find supporters among system theoreticians. For instance, Cohen (1992) suggested that, "*it is not possible to speak of the command neurons driving the CPG since they are both driving each other. As a consequence of the mutual interaction within the system, each portion of the system contributes its own peculiar properties and constraints to the final output.*" Moreover, Thelen & Smith (1996) argued, "*the notion of the CPGs as the essence of locomotion does not fit the data… They simply do not account for what we really observe in developing organisms… The fact of development is not explained by a list of innate ideas. Just as the assumption of a built-in CPG does not explain the development of walking.*" The CPG was considered to be a "motor program" by some experimental psychologists. Rosenbaum & Saltzman (1984) explained the motor program as, "*before the execution of a sequence of voluntary movements, a memory representation for instructions for the entire sequence is thought to be established in the central nervous system … (p.51). The motor program construct has not successively accounted for the hallmark of human intentional actions: their functional adaptability (p.74). …both the CPG and the motor program… consider movement to be generated by 'pure' neural commands" (p.75).* In this context, Thelen and Smith (1994) stated that, "*Real data from real frogs, chicks, cats, and humans render the construct of the CPG illusory… the motor program construct has not successively accounted for the hallmark of human intentional actions: their functional adaptability. If the motor program contains the instructions for the entire sequence of behaviors ahead of time, how can novel and adapted forms be generated?*" (p.74). On the other hand, the CPGs are not static, previously hard-wired, firmly organized systems, but instead are rather loosely organized systems under the influence of

the steadily changing chemical or sensory control, with newly emerged functional circuits (Selverston, 1988, cited by Kelso, 1995, p.243). Consequently, they exhibit one of the principles of biological self-organization, i.e., different neural networks can induce similar outcomes (tasks), while similar neural networks can produce different outcomes (tasks) (Marder, 1988, cited by Kelso, 1995, p.243). *"Still others are ready to give up, or at least expand the (no longer recognizable) CPG concept to that of a motor pattern network" (Kelso, 1995, p. 243).* A neuronal network such as a CPG can change itself according to current conditions and exhibit transitions between functional states, resulting from dynamic instabilities in the system with dynamic interactions at neuronal, synaptic and network levels. *"At such transitions, self-organization becomes apparent: new and different patterns arise as cooperative states of the coupling among neural elements"* (Kelso, 1995, p.243).

10. Concluding remarks

Uner Tan syndrome (UTS), discovered in 2005 in Southern Turkey, mainly consists of habitual quadrupedal locomotion, mental retardation, and dysarthric or no speech, with or without cerebello-vermial hypoplasia and mildly simplified cortical gyri. A man walking on all four extremities, probably exhibiting the symptoms of the UTS, was first discovered and reported in 1917, nearly a hundred years ago, by a British traveler on the Middle Black Sea coast, near Samsun, on the famous Baghdad road, during the time of the Ottoman Empire. Between 2005 and 2010, 10 families with 33 cases—13 women (42.4%) and 19 men (57.6%)—were discovered in Turkey (see Table 1). In addition, there were two male children (4 and 12 years old) resident in Adana and Istanbul, who were normal in cognitive abilities, with no neurological signs and symptoms, and normal brain MRIs, but with facultative quadrupedal locomotion. Including the cases from Brazil, Iraq, Mexico, and Chile, there were 25 men (64.1%) and 14 women (35.9%) around the world. Statistics showed that the number of men significantly exceeded the number of women ($p<.05$), suggesting a male preponderance in UTS. Genealogical analysis suggested autosomal recessive transmission linked to chromosome 17p13.1.13.3 with a missense mutation in the WDR81 gene in the affected members of the first described Iskenderun family. Homozygocity was found in two families resident in remote villages of Southern and Northern Turkey, and was mapped to a region on chromosome 9p24 that included the very low density lipoprotein receptor gene, VLDLR. These results suggested that UTS may be a genetically heterogeneous syndrome. Interestingly, the mother of the affected siblings in the Iskenderun family had Type-I diabetes, which may be associated with congenital malformations such as caudal regression in mice, suggesting that the maternal diabetes in some cases with UTS could be associated with neuronal damage, resulting in impaired balance.

UTS can be considered within the framework of the non-progressive autosomal recessive cerebellar ataxias, which are associated with various genetic mutations. Among these conditions, such as disequilibrium syndrome (DES), Cayman ataxia, and Joubert syndrome, there are overlapping symptoms, like truncal ataxia, psychomotor delay, and dysarthric speech. All of these syndromes show genetic heterogeneity, which is characteristic for many diseases. Thus, genetics alone do not seem to be informative for the origins of many syndromes, including UTS. From the viewpoint of dynamical systems theory, there may not be a single factor including a genetic code that predetermines the emergence of human quadrupedalism, seen, for instance, in UTS. Rather, it may involve a self-organization

process, consisting of many decentralized and local interactions among neuronal, genetic, and environmental subsystems.

UTS was divided into two subgroups: Type-I and Type-II, the former exhibiting no hypotonia, and the latter being associated with early hypotonia. The comparison with other closely related syndromes, such as DES, Cayman ataxia, and Joubert syndrome, indicated that UTS may be distinguished from these syndromes by habitual locomotion on all four extremities, normal stature, and normal muscle tone in Type-I cases, but early hypotonia in Type-II cases. For these reasons, UTS may be considered a distinct entity among the cerebellar ataxias.

The most remarkable characteristic of UTS is diagonal-sequence quadrupedal locomotion, similar to the non-human primates and contrary to non-primate species. The evolutionary advantage of diagonal-sequence quadrupedal locomotion is not known. However, interestingly, there seems to be an evolutionary advantage of this type of locomotion for primate evolution, with regard to the emergence of complex neural circuits with related highly complex structures. Namely, only primates with diagonal-sequence quadrupedal locomotion followed an evolution favoring larger brains, highly developed cognitive abilities, highly developed hand skills, and language, with erect posture and bipedal locomotion, creating the unity of human beings. The non-primate mammals using lateral-sequence quadrupedal locomotion did not show a similar phylogenetic progress compared to those with diagonal-sequence quadrupedal locomotion, which, in essence, was the phylogenetically oldest type of locomotion since it was a characteristic of the first tetrapods during the Devonian period. This suggests that the ancestral neural networks responsible for the diagonal-sequence quadrupedal locomotion were reserved for at least nearly 400 million years since the Devonian tetrapod-like fishes.

The human quadrupedal locomotion seen in UTS showed some similarities with non-human primates. For instance, the human quadrupeds supported their body weight more on the feet than on the hands during quadrupedal locomotion, in a similar way to the weight distribution during location in most non-human primates. In contrast, non-primate quadrupedal mammals usually support their body weight more on the forelimbs than their hind limbs. The body weight support patterns in non-human and human primates suggests that the reduced body weight on hands than feet would be beneficial for the development of fine hand skills in primates. The complete freeing of hands in human beings during upright walking would be entirely associated with highly developed hand skills compared to the non-human primates walking on all four extremities.

It was suggested that UTS may be considered a further example for Darwinian diseases, which may be associated with an evolutionary understanding of the disorders using evolutionary principles, such as natural selection. In this context, UTS may also be considered a disease with phylogenetic regression. In some UTS cases, the supraorbital tori were remarkably prominent, and were more or less similar to those in non-human primates. This was taken to be an ancestral feature, in addition to the diagonal-sequence quadrupedal locomotion, and the body weight being supported predominantly by the hind legs.

Human quadrupedalism was proposed to be a phenotypic example of evolution in reverse, i.e., the reacquisition by derived populations of the same character states as those of ancestor

populations. On the other hand, UTS may be considered within the framework of phylogenetic diseases (phylogenetic regression), which may be related to the phenotypic backward evolutionary atavism (the reappearance of a lost character (either morphological or behavioral) that was typical of remote ancestors). The habitual diagonal-sequence quadrupedal locomotion, standing with bent knees and bent trunk (flexor posture contrary to the extensor posture in modern human beings), prominent supraorbital tori, fist walking with bent fingers, and non-opposable thumb, may be related to ancestral characteristics in the UTS cases. The diagonal-sequence quadrupedal locomotion (habitual or facultative) was also the preferred gait of some individuals with entirely normal brains, probably as a result of the neural networks preserved during nearly 400 million years of evolution.

The emergence of human quadrupedalism was related to the self-organizing processes occurring in complex systems, which selects or attracts one preferred behavioral state or locomotor trait out of many possible attractor states. Since this is a spontaneous and unpredictable event, behavioral variability being a common precursor, the dynamic systems provide enormous flexibilities. According to the interactions of the internal components with their sensitivities to external conditions, the complex dynamical systems prefer a behavioral mode or modes. Concerning the locomotor patterns, the dynamical systems (brain and body) of the developing child may prefer or create some kind of locomotion, according to interactions of the internal components and environmental conditions, without a direct role of any causative factor(s), such as genetic or neural codes. This self-organization occurs through the interactions of its components, endogenously (within the brain), and/or exogenously through some environmental influence, but without any external force.

The emergence of human locomotion is a developmental event in which the self-organization processes play the major role, suggesting no innate or previously prescribed codes are essential for the emergence of walking during locomotor development. The developing skeleto-motor system of the individuals with impaired balance may self-organize, which is itself triggered by the exogenous environmental constraints, and they will then find the most suitable and most comfortable, and hence preferred, mode of locomotion, spontaneously generating novel and organized forms and attractor states. In UTS, these spontaneous, unpredictable strange attractors may include diagonal-sequence quadrupedal locomotion, as also seen in the non-human primates, or an entirely unpredictable novel quadrupedal locomotion may emerge, such as the inverse (face-up) quadrupedal locomotion. More examples of the unpredictable, self-organized, and emergent strange attractors were presented in this article. The contribution of the single factors such as the genetic and/or neural codes (central pattern generators) to the emergence of the locomotor patterns during locomotor development were rejected, considering the current scientific research in these fields, consistent with the concept of self-organization, suggesting no single element has causal priority.

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