Chapter 4

Humans Walking on All Four Extremities With Mental Retardation and Dysarthric or no Speech: A Dynamical Systems Perspective

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Quadrupedal locomotion (walking on four extremities)

Locomotion is the movement of an organism from one place to another, often by the action of appendages such as flagella, limbs, or wings. In some animals, such as fish, a lumbering locomotion results from a wavelike series of muscle contractions (The American Heritage® Science Dictionary, 2005). Walking is travelling by foot; gait is the manner of locomotion; running is the act of travelling on foot at a fast pace; crawling is a slow mode of hand-knee or hand-foot locomotion. Walking on all four extremities (quadrupedal locomotion, QL) is the trait of the quadruped animals. Non-primate mammals usually utilize lateral-sequence QL, in which the hind limb touchdowns are followed by the ipsilateral forelimb touchdowns (symmetric gait). On the contrary, the non-human primates usually utilize a diagonal-sequence QL, in which the hind-limb moves with the contralateral forelimb in a diagonal couplet (asymmetric gait). Interestingly, only the animals exhibiting the diagonal-sequence QL with symmetrical gait evolved towards species with enlarged brains associated with highly complex neural circuits, till the emergence of human beings. The animals exhibiting lateral-sequence QL did not show such a phylogenetic progress compared to those with diagonal-sequence QL. Figure 1 shows the differences between lateral-(left) and diagonal-sequence (right) patterns of QL.

1.2. Evolutionarily preserved neural networks for QL

With regard to the origins of the diagonal-sequence QL, it is reasonable to conclude that the neural circuits for this kind of locomotion existed even in the most primitive tetrapods, lived

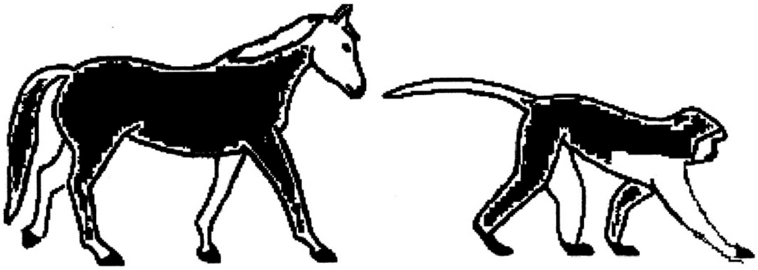

Figure 1. Difference between walking styles of primate (right) and non-primate (left) mammals. Most non-primate animals utilize lateral-sequence locomotion, but most primates utilize diagonal-sequence locomotion. Notice the filled *vs* unfilled extremities during lateral (left) and diagonal (right) locomotion and the interference between the fore- and hind limbs on the left side during diagonal gait.

in the Devonian period during transition from water to land. Thus, this type of locomotion is indeed phylogenetically the oldest locomotor trait, not the lateral-sequence QL. Namely, fossils due to the first fish-like tetrapods, lived approximately 395 MYA, were recently discovered on the Polish coast. From the fossil tracks left by a tetrapod, it was concluded that this most primitive quadruped animal walked with diagonal strides (see Figure 2), reflecting the lumbering locomotor movements as their ancestors lived in marine environments [1]. Interestingly, the quintessence of this diagonal-sequence coordination of the extremities during QL, did not change throughout the course of evolution, through salamanders and tuataras [2], to the emergence of non-human primates and even human beings during upright locomotion on two extremities [3, 4]. On the other hand, these results also suggest that the neural circuits responsible for the diagonal-sequence QL have been preserved for about 400 million years since the first emergence of QL in the fishlike tetrapods. In accord, the lumbering locomotor movements of tetrapods may even be visualized in human infants during crawling (see Figure 3), reasonably resulting from the activity of the ancestral neural networks still functioning approximately 400 million years later from the first emergence of the fishlike tetrapods. In accord, there are reports in the scientific literature supporting these considerations, i.e., the neural networks controlling the diagonal-sequence QL have been preserved throughout the evolutionary development for at least 395 million years since the emergence of the tetrapod-like fishes lived during the Devonian period [1,5,6].

As mentioned above, the neural networks playing a role in the emergence of the QL have been preserved for at least 395 million years since the Devonian tetrapod-like fishes [1]. Accordingly, it was reported an evolutionarily conserved daldh2 intronic enhancer in the frog, mouse, and chicken, being also involved in the formation of the neural tube throughout vertebrate species [7]. This evolutionary conservation of the enzyme playing a role in shaping the neural tube is essentially related to the evolutionary conservation of the neural networks for the diagonal-sequence QL. The mechanisms of this evolutionary preservation of the basic neural networks remain, however, unresolved. The genetic and/or epigenetic mechanisms contributing to the evolutionary development would shed some light on this subject.

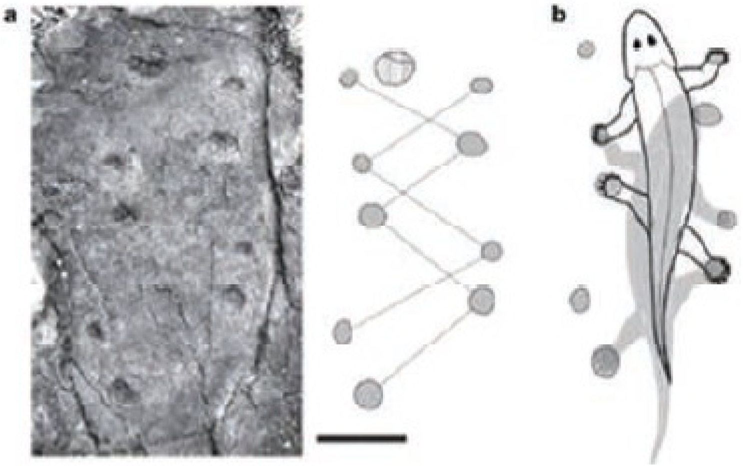

Figure 2. The trackway on the left (a) shows the hand and foot shapes in a diagonal stride pattern with a generic Devonian tetrapod fitted to this tackways (b). Notice the lumbering diagonal-sequence QL of this tetrapod, similar to its ancestral forms living in water.

2. Human beings with QL; Üner Tan Syndrome (UTS)

2.1. History

A human being habitually walking on all four extremities (quadrupedalism) was first discovered by Childs [8], the notable British traveler and writer, nearly a hundred years ago, on the famous Bagdad road near Havsa/Samsun on the middle Black Sea coast, at time of Ottoman Empire. This man probably belonged to a Greek family, since this region was populated by Greeks during this time. And, he probably was the son of a consanguineous family living in this closed Greek population with a high probability of consanguineous marriages. Childs described this man on page 29 of his book as follows:

> "As we rose out of the next valley a donkey and a figure on the ground beside it attracted my attention…the figure moved in a curious fashion, and I went up to look more closely. And now it appeared I had fallen into the trap of a beggar…He sprang up and asked for alms, and because there 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."

Fig. 4 shows the man walking on all four extremities reported in 1917 for the first time in the scientific literature by Childs, a famous British traveler and writer.

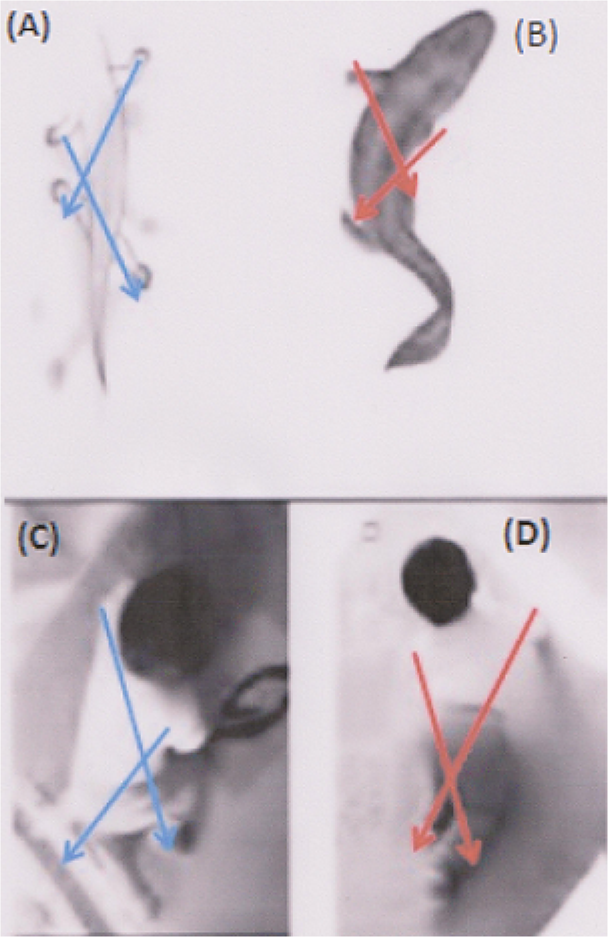

Figure 3. Diagonal-sequence QLs (see arrows) with lumbering in a generic Devonian tetrapod during the time of transition from water to land (A), proposed picture of a most primitive tetrapod, *Acanthostego,* with lumbering diagonal-sequence QL, a half fish, half reptile, lived in a swamp, 360 million years ago (MYA), see B. C, D: a contemporary human child crawling on all fours with accompanying lumbering movements, more or less similar to the very primitive Devonian animal lived almost 400 MYA.

Since the first discovery of a man with quadrupedalism, in 1917, not a similar human being was reported in the scientific literature, until the first description of five consanguineous kindred, resident in Southern Turkey, who exhibited a symptom complex with habitual QL, mental retardation, and dysarthric speech with limited conscious experience [9-15]. This pointed out a novel syndrome, which was referred to *Uner Tan Syndrome (UTS)* in some books, book chapters, and journal articles, accentuating the discovery's name. This novel syndrome was first reported, in 2005, in front of the members of the Turkish Academy of Sciences, in Ankara and Istanbul [9,10], also being published in some Turkish and English journals [11-15,

Figure 4. First man habitually walking on all four extremities, who was first discovered in Turkey during Ottoman Empire, in 1917, by Childs, the famous British traveler and writer, in Havsa/Samsun, Middle Black-Sea coast. The man was standing beneath his donkey, carrying torn trousers and shirt, pointing out his poverty.

see for reviews [16, 17]. This remarkable syndrome soon sparked a world-wide interest (see for reviews [18,19,], mainly because of its relation to human evolution.

2.2. UTS type-I and type-II

According to the childhood hypotonia in skeletal muscles, two subgroups of cases exhibiting the UTS could be distinguished: (i) UTS Type I, which included UTS cases without childhood hypotonia. Of 32 cases hitherto discovered in Turkey, 25 (78.1%) patients had UTS Type I. (ii) UTS Type II, which included UTS cases with childhood hypotonia. This was observed in 7 (21.9%) cases, who had no early ambulation during childhood. However, the childhood hypotonia disappeared and replaced with normal muscle tonus accompanied with QL during adolescence (see for reviews [16,17]. Figure 5 illustrates some of the UTS Type-I cases exhibiting diagonal-sequence QL, with coincidence of limbs and feet on the same side (interference effect), which would be disadvantageous for proper walking and running on all four extremities.

2.3. Forelimb and hind limb weight supports during QL

Non-primate mammals usually support their body weight more on the forelimbs than their hind limbs during QL [20,21]. Contrarily, most primates support their body weight more on their hind limbs than their forelimbs during QL [20,22,23]. The decreased forelimb weight support in non-human primates was interpreted as an adaptation to reduce stress on the forelimb joints, and facilitate the forelimb motility, especially for arboreal locomotion [24,25]. However, the human beings with QL without arboreal habits showed similar body mass distribution on the footfall patterns, i.e., less support on their hands (24% of their body weight) than their feet (76.0% of their body weight). Similarly, monkeys also support less than 30.0% of their body weight on their forelimbs [24,26,28]. According to Reynolds [24], 30-45% of the body weight was exerted on the forelimbs during QL of eight primates. Thus, the human beings with habitual QL also support their body weight more on their hind limb than their forelimbs, like their close relatives, the non-human primates. This body weight support pattern on hands and feet in human quadrupeds is consistent with the hypothesis that less body weight exerted on the hands than on the feet would be beneficial for fine manual skills in primates. A complete freeing of hands of human beings due to upright walking would be entirely associated with their highly developed hand skills and their accompanying co-development of their brains, all resulting from the replacement of a weight carrying function with a cognitive function of human hands. The severe mental retardation associated with the habitual QL in UTS cases could, therefore, be considered as an evolutionary example for the coupling between locomotor and mental abilities. The close coupling between the manual skill and cognitive ability was previously reported in humans [29-31] and great apes [32], consistent with Tan's psychomotor theory [33].

Figure 5. UTS cases walking on all four extremities exhibiting diagonal-sequence QL. Notice the interference between arms and legs on the same side due to diagonal sequence QL. Straight lines, forward and dotted lines, backward motions of the contralateral extremities.

2.4. Neurological examinations

All of the UTS-cases could understand simple questions and demands, but 24 cases (75.0%) in 7 families had no expressive speech at all, so that they replied the simple questions with one or two simple sounds. Only 8 cases (25.0%) had a dysarthric speech with a very limited vocabulary. Cognitive tests showed a severe mental retardation in all cases. Brain MRI scans revealed a cerebello-vermial hypoplasia with mild gyral simplification in cerebral cortex, except one case with normal cerebellum and impaired peripheral vestibular system instead of the central vestibular system in other cases. Truncal ataxia was present in all cases, but muscle tone was normal with strong arms and legs in these adult cases. The results of the neurological examinations, MRI and PET scans, and cognitive tests were presented in two review articles [16,17]. The clinical characteristics of the affected cases of the families from Turkey are summarized in Table 1.

2.5. Gender differences

There were 19 men and 13 women with UTS from Turkey, 2 men and 1 women from Morocco, 4 brothers from Brazil, 2 men from Iraq, 1 man from Mexico and 1 man from Chile. The number of men (n = 29, 67.4%) exceeded that of women (n = 14, 32.6%), the difference (34.8%) being, however, only marginally significant ($\chi^2 = 3.34$, df = 1, p =.07).

2.6. Cognitive tests

All of the patients exhibited severe mental retardation, according to the results of two cognitive tests. "Mini Mental State Examination Test" (MMSE), also known as the "Folstein test" [34], consisting of a 30-point questionnaire, testing for the individuals' attention, calculation, recall, language and motor skills, showed severe mental retardation in all of the cases (range = 0 to 2 points). The healthy siblings of the affected individuals were relatively normal in the MMSE test, with scores ranging between 25 and 29 points, although tey all shared the same environment. The Wais-R (Wechsler Adult Intelligence Scale-Revised) showed also severe mental retardation in the UTS cases, who obtained "0" to "4" points of a total 30 points. The results of the MMSE test are summarized in Table 2.

2.7. Genetics

The UTS is genetically heterogeneous. Namely, we found missense mutations in the following genes: VLDLR in Canakkale and Gaziantep families [35], WDR81 in Iskenderun family [36], ATP8A2 in Adana family [37]. Interestingly, the mother of the affected siblings in the Iskenderun family had type-I diabetes, which may be associated with developmental malformations, such as caudal regression in mice [38]. The VLDLR gene is involved in the controlling neuroblast migration in the developing central nervous system, see [35]. This gene shows an evolutionary conservation for at least 200 million years [39]. WDR81 gene is evolutionarily highly conserved trans-membrane protein, which is highly expressed especially in cerebellum and corpus callosum, see [36]. However, different mutations in a single gene may lead to different expressions of the same phenotype (allelic heterogeneity). Moreover, *similar genetic*

Findings	**Iskend.** **Type-I**	**Adana** **Type-I**	**Antep** **Type-I**	**Canak.** **Type-I**	**Kars** **Type-I**	**Afyon** **Type-I**	**Diyarb.** **Type-II**
N (QL)	6	3	7	4	2	3	7
Men	2	2	5	2	2	2	4
Women	4	1	2	2	0	1	3
Age	21-35	29-39	14-48	24-64	44-45	12-24	9-27
Mutation	17p.13	13q.12	9p.24	9p.24	(?)	9p.24	(?)
Ves.Imp.	Central	Pripheral	Central	Central	Central	Central	Central
Cerebel.	Hypopl.	Normal	Hypopl.	Hypopl.	Hypopl.	Hypopl.	Hypopl.
Vermis	Hypopl.	Normal	Hypopl.	Hypopl.	Hypopl.	Hypopl.	Hypopl.
Cer.cort.	Gy.simp	Normal	Gy.simp	Gy.simp	Gy.simp	Gy.simp	Gy.simp
DTR upp	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Strength	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Babinski	+ (3/6)	Absent	+ (3/7)	Absent	+ (1/2)	+ (1/3)	+ (1/7)
Tremor	Mild	Mild	+ (1/7)	(-)	(-)	(-)	(-)
Nystag.	(+)	(+)	(-)	(-)	(-)	(-)	+ (2/7)
E.Hypoto	(-)	(-)	(-)	(-)	(-)	(-)	(+)
Men.ret.	Severe	Severe	Severe	Mild	Severe	Severe	Severe
Speech	Dysarth.	Dysarth.	No	No	No	No	No
Standing	Yes	No (1/3)	Yes	Yes	Yes	Yes	Yes
Bip.walk	(+)	(-):(1/3)	(+)	(+)	(+)	(+)	(-):(1/7)

Table 1. Findings from families with UTS. Iskend.: Iskenderun (mutation in WDR81 gene), Adana (mutation in ATP8A2 gene), Canak.:Canakkale (mutation in VLDLR gene), Afyon (mutation in VLDLR gene), Diyarb.:Diyarbakir. Ves.Imp.:vestibular impairment; Cerebel.:cerebellum; Cer.cor.: cerebral cortex; DTR upp.: upper extremity deep tendon reflexes; DTR low: lower extremity deep tendon reflexes; M.tone: muscle tone; Nystag.:nystagmus; E.hypoto.: extremity hypotonia; Men.ret.: mental retardation; Bip.walk.: bipedal walking.

lesions can have entirely different phenotypes [40]. Thus, mutations in a single gene like VLDLR cannot be solely associated with quadrupedal locomotion in human beings. Given the genetic heterogeneity of the UTS, a specific gene directly responsible for the emergence of human quadrupedalism does not seem to be reasonable. Moreover, the missense mutations found in the affected cases may also be involved in neural functions other than the QL. Accordingly, missense mutation in VLDLR gene was also associated with congenital cerebellar hypoplasia [41], along with Norman-Roberts syndrome, characterized by microcephaly, hypertonia, hyperreflexia, severe mental retardation, and agyric cerebral cortex [42]. The VLDLR gene works with a protein, reelin, which is also associated with disorders such as Alzheimer's disease, schizophrenia, and bipolar disorder.

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 in time:*** They gave unrelated answers such as 80,90,house,cow,dog, or did not give an answer at all, except thinking.
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, cow, dog, mother, father, etc.
Repeat:ball,flag,tree	***Immediate recall:*** Only a few of them could recall these words.
Count backwards from 100 by 7	***Attention:*** They even could not count forwards from 0 to 10.
Recall 3 words I asked previously	***Delayed verbal recall:*** Nobody could recall the words previously asked
Name these items: watch, pencil	***Naming:*** Only some of them could name these items
Repeat following: No if, ands, or buts	***Repetition:*** Nobody could repeat them
Take the paper in your hand, fold it in half, and put it on the floor.	***3-stage command:*** Nobody could follow this command, and only some of them took the paper in the hand.

Table 2. Questions from the MMSE test and patients' answers.

Merlberg et al [43] re-evaluated the disequilibrium syndrome [44] in Swedish patients with non-progressive cerebellar ataxia, dysarthria, short stature, childhood hypotonia, and mental retardation, without VLDLR mutation. Interestingly, MRI showed a spectrum from normal to severe cerebellar hypoplasia. Similarly, the UTS cases of the Adana family did not exhibit cerebellar hypoplasia [13-15], despite a missense mutation in the ATP8A2 gene [37], suggesting no genetic association of the cerebellar hypoplasia in UTS.

Taking together, the genetic associations hitherto reported for the UTS seem to have no or only minor explanatory power, if any, for the origins of human quadrupedalism. In accord, Hall [45] argued how genetics failed to find solutions for the discrepancies concerning the so-called genetic diseases: *evidence is growing that your DNA sequence does not determine your entire genetic fate.. Larger scale genomic studies over the past five years or so have mainly failed to turn up common genes that play a major role in complex human maladies.* This argument seems to be also true for well-known disorders including diabetes, schizophrenia, and cancer, as Maher [46] stated:

even when dozens of genes have been linked to a trait, both the individual and cumulative effects are surprisingly small and nowhere near enough to explain earlier estimates of heritability.

3. Darwinian medicine; UTS

Why are only some rare cases predisposed to walk on all four extremities similar to our early ancestors? The quest to find an answer to this and similar questions was the starting point for establishing a new discipline, *"Darwinian medicine"*, which is a novel concept providing a foundation for all medicine [47]. The aim of the Darwinian medicine is the evolutionary understanding of aspects of the body with regard to its vulnerability to disease(s), as Zampieri [47] stated: *It tries to find evolutionary explanations for shared characteristics that leave all people vulnerable to a disease.* Evolutionary or Darwinian medicine may be useful to understand better why diseases exist despite natural selection [48,49]. A number of diseases were considered as Darwinian disorders, such as tuberculosis, Huntington's disease, depression, obesity, anxiety, pain, nausea, cough, fever, vomiting, fatigue, epilepsy, obsessive compulsive disorder, and schizophrenia [50-53]. In this framework, the UTS with the reappearance of the ancestral features such as quadrupedal locomotion and primitive cognition including no speech in most of the cases, and severe mental retardation may also be considered as a further example related to Darwinian medicine.

Rapoport [54] first introduced the concept of *"phylogenic diseases"*, such as Alzheimer's disease as a "phylogenic regression", comparing brain aging involution to the reversed phenomenon of Darwinian evolution [55. Accordingly, many neurodegenerative diseases such as Parkinson's disease, schizophrenia, Alzheimer's disease, and many highest level gait disorders including the UTS with ancestral QL, i.e., the re-emergence of old automatism of pre-human gait, may also be considered under these phylogenic diseases. In this context, the recently introduced paleoneurologic standpoint may help us to more deeply understand the pathogenesis of the neuropsychiatric diseases, provided that they are re-considered under evolutionary perspective.

4. Complex systems; Self-organization

The word "complex" may be defined as "consisting of interconnected or interwoven parts" [56]. Many complex systems have the tendency to spontaneously generate novel and organized forms, such as ice crystals, galactic spirals, cloud formation, lightning flashes in the sky, or polygonal impressions in the earth. The spontaneously generated formation in the nature are in no way designed by anything, not even by natural selection, being entirely the art of nature with self-organizing properties within complex systems, following the principle, *the sum of the parts is greater than the parts taken* *independently,* Contrary to Isaac Newton's arguments, …*the whole is the sum of all the parts..*

Complex systems have a strong tendency to self-organize, i.e., spontaneous formation of patterns in open nonequilibrium systems. This is also the quintessence of all living systems.

For instance, insects can spontaneously build their nests or hives, hunt in groups, and explore the food resources in their environment. The evolution of the biological forms and structures may also be associated with self-organization. Some authors have even questioned the centrality of natural selection in evolution, since Darwinism essentially ignores the principles of self-organization. Accordingly, Oudeyer [57] argued: *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 rom generation in which self-organization plays a central role.*

Self-organization is closely coupled with "emergence", a fundamental property of complex systems, which is the unpredictable product of the system, resulting from interconnections and interactions between parts of a dynamical system; entities, interactions, and the environment are key contributors to emergence [58]. The main characteristic of the UTS, human quadrupedalism, may also be an emergent property of the locomotor development. In accord with the dynamical systems theory, and the principles of self-organization, it can be stated that no genetic or neural code may be the causative factor for the emergence of the human quadrupedalism. As mentioned above, we could not isolate a single gene responsible only for the QL in human beings, minimizing the role, if any, of any genetic code in the emergence of human QL.

Human quadrupedalism may be considered as a strange attractor, a state of a dynamical system toward which that system tends to evolve. For instance, the EEG may exhibit one type of strange attractor while a person is at rest, but another type of strange attractor during mathematical thinking. The common property of strange attractors is their unpredictability. The rarely occurring locomotor pattern in the UTS cases, i.e., QL, may be related to its unpredictability as a strange attractor. An entirely different locomotor strange attractor emerged in a man from Tanzania, who exhibited all of the symptoms of the UTS, including truncal ataxia and no upright ambulation with mental retardation and no speech. However, an entirely novel and unpredictable locomotor pattern emerged in this man as a strange attractor. Namely, his QL was upside down, i.e., in face-up position. He used his hands and feet for QL, but used palms and heels instead of the soles (see Fig. 6). This is the first reported case exhibiting the UTS with inverse QL.

In essence, the dynamical systems tend to control the outcome of the system to find which patterns can possibly be built from the systems components to begin with, and the structural constraints of the environment, the self-organizing phenomena being basic mechanisms for the emergence of any adaptive behavior, such as the adaptive self-organization phenomena playing a role in the developmental emergence of the human quadrupedalism.

Figure 6. Tanzanian man with UTS, walking on all four extremities but with inverse quadrupedal locomotion: further example for a locomotor strange attractor.

5. Central Pattern Generators (CPG)

The locomotor system is closely related to CPGs embedded in the spinal cord, which is a set of motoneurons responsible for locomotion [59], probably also involved in the human QL. The spinal motor system seems to be similar in all quadrupeds and human beings [4]. Individuals with or without UTS may all share the same neural networks responsible for the diagonal-sequence quadrupedal locomotion as the nonhuman primates, because they all are using the common neuronal control mechanisms for locomotion [60]. However, the CPGs do not reflect the coordinated walking pattern in intact animals, since there are separate CPGs for each leg in the cat [61]. On the other hand, the presence of the CPGs in higher primates is much less convincing. This could be due to the increased role of the corticospinal tractus in primates, suppressing the spinal motor circuitry responsible for relatively rough locomotor movements, and facilitating the skilled hand movements. According to Duysens et al [61], CPGs have no direct equivalent in human beings.

The concept of CPGs did not find supporters among system theoreticians. For instance, Thelen and Smith [62] 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. These authors further stated that real data from real frogs, chicks, cats, and humans render the construct of the CPG illusory.. If the program contains the instructions for the entire sequence of behaviors ahead of time, how can novel and adapted forms be generated? Actually, the CPGs exhibit one of the principles of biological self-organization as dynamic entities, i.e., different neural networks may induce similar outcomes, while similar neural networks can produce different outcomes. Namely, the CPGs are not static, previously hard-wired, firmly organized neural networks, they are rather loosely organized systems under the influence of the steadily changing chemical or sensory control, with newly emerged functional circuits [63]. Moreover, Neuronal networks within CPGs can change itself according to current conditions and exhibit transitions between functional states, resulting from dynamic instabilities occurring within the system with dynamic interactions at the neuronal, synaptic, and network levels [63].

6. Maturation theories

The concept of motor development showed a gradual shift from the traditional neuronal maturation theory towards the dynamic systems theory. It was believed, in the mid-1990s, that the development of the central nervous system occurred through the genetically predetermined neural networks and spinal reflexes, under the control of the cerebral cortex. Accordingly, the locomotor actions such as standing and walking in infants would result from the gradual maturation of the CNS under the influence of the cerebral cortex, not learnt by experience. The traditional maturation theory utilized the longitudinal studies to show the developmental sequence of motor behaviors in infants and young children. This was mainly elaborated by Gessel [64], Shirley [65], and McGraw [66,67], who searched for rules governing the order of changes during motor maturation. Konner [68] stated that *motor development sequences are largely genetically programmed.* The development of early motor behaviors was attributed to the maturation of the cortico-spinal pathways [69,70]. Despite some valuable information gained from the traditional maturation theory, it was far from explaining the dynamics of locomotor development. In this context, Ulrich [71] argued that *it is not at all clear how genetic codes can be translated into even simple patterned neural organization…behavior is much more than a simple neural pattern* (p.321).

Contrary to the traditional maturation theories, the contemporary approaches considered the properties of complex systems with many dynamically interacting subcomponents, to be able to solve the problems related to locomotor development. This dynamic systems theory considers the behavior of a system, not by taking it as separate parts, but by taking these parts to see under which circumstances they dynamically cooperate to produce the whole behavioral pattern such as locomotor functions. According to the dynamic systems theory, the behavioral patterns can emerge from the dynamic interactions of multiple subsystems; genetic or neural codes are not represented *a priori* in the brain, nor are locomotor patterns, such as walking and running. The emergence of locomotion is a self-organizing process, as in other complex systems. According to Ulrich [71, p.324], *the coordination pattern emerges spontaneously and is self-organized and opportunistic.* Taking together, there are two major but current and conflicting theories involved in the development of locomotor control: neuronal maturationist theory and the dynamic systems theory. According to the first theory, the maturation of the CNS occurred through the genetically predetermined neural networks; the locomotor development results from progressively maturated and hence increased cortical control on the spinal reflexes. Controversially, however, the system theoreticians did not accept the neural-maturationist theories, asking how can the timetable of motor solutions be encoded in the brain or in the genes. Accordingly, Kelso et al [72] utilized the dynamic systems theory to better explain the developmental emergence of locomotion in human beings. These authors argued that a behavior, such as a locomotor pattern may result from the combined dynamic actions of, for instance, muscle strength, body weight, postural support, motivation, and brain development, in addition to the environmental initial conditions and task requirements.

7. Neuronal group selection theory

In addition to the neuronal maturation theory and the dynamic systems theory, there is a third theory, the neuronal group selection theory (NGST) [73], which combines the “nature” part of the neural-maturationist theories with the “nurture” part of the dynamic systems theory. The neuronal groups are collections of many neurons interconnected by excitatory and/or inhibitory synapses as well as recurrent feedback circuits. According to the NGST, the structural and functional characteristics of these neuronal groups are determined by evolution. During locomotor development, behavior and experience produce afferent information for the central nervous system, which is used for the neuronal selection, according to the strength of the synaptic connections. The changed connectivity allows for a situation-specific selection of neuronal groups, which can be adapted to environmental constraints. The NGST emphasizes the role of the complex information processing originating from an intertwining of information from genes and the environment. This is not consistent with the “nature-nurture” debate. During motor development in early fetal life, the spontaneous fetal movements (primary variability), i.e., the self-generated motor activity with the consequent self-generated afferent information, may explore all the locomotor possibilities within the neurobiological and anthropometric constraints within the CNS, preserved during evolution.

During postnatal development, all of the intentional motor behaviors are within the frame of “primary variability”. The neuronal networks emerging during this developmental phase, especially prominent in the cerebral cortex are suitable for the selection of the appropriate locomotor circuits, responsible, for instance, for the infantile crawling. The most effective motor pattern gradually emerges following exploratory continuous information processing within the CNS. The time-sequence for the selection process changes with function, for instance, the second half year after birth for arm reaching. The postural activity of neck and truck muscles are direction specific before infants cat sir independently at about five months after birth. The most efficient selection for the postural balance occurs around 12-18 months of age.

The long duration of the developmental processes suggests that long-lasting motor experiences are needed for the establishment of the secondary neuronal networks. This may be associated with the late-onset quadrupedalism in some UTS cases [74]. Actually, exercise may be beneficial for the selection of the most effective neuronal pattern, by reducing the amount of secondary variation [75]. The reverse occurs in the absence of exercise, similar to the UTS cases without exercise at all.

The NGST for the locomotor development is closely related to the concept of the adaptive self-organization. Namely, the developmental selection is the differential survival of developmental units, which was proposed as an explanation for examples of self-organization [76].

8. Dynamics of locomotor development in humans

The contemporary views on the ontogenic development of locomotor skills accentuate the role of the self-organizing processes within the scope of complex systems. As mentioned above, the neural patterns playing a role in the emergence of the diagonal-sequence QL have existed since about 400 MYA during the Devonian period, having arisen with the first appearance of the ancestral tetrapods. That is, this type of locomotion is indeed phylogenetically the oldest locomotor trait of tetrapods. Interestingly, the quintessence of this locomotor activity did not change during evolution through salamanders and tuataras [2], till the emergence of non-human primates and even human beings exhibiting diagonal-sequence movements between arms and legs, even during their upright walking [3]. It may thus be concluded that the neural generators responsible for the diagonal-sequence QL may already be present in the complex locomotor systems of primates, including humans. Taking together, it may be argued that the neural patterns responsible for the QL in human beings may emerge through exploration of available solutions within the CNS, such as the ancestral neural generators for the QL and then selection of preferred patterns, such as the CPGs [77-79]. Following this ontogenetic theory, it may be concluded that the emergence of the diagonal-sequence QL in human beings may be the result of a prenatal exploration and subsequent neuronal group selection process following the principles of the self-organizing dynamic systems [80].

The cases exhibiting UTS seem to be unable to make the secondary selection for the neural networks appropriate for bipedal locomotion during infantile development. That is, they could not make the transition from the infantile stage of crawling on all fours to upright standing and bipedal walking. Their brain apparently explored the possible solutions for locomotion, but could not select the neural patterns for bipedal locomotion, because of the structural anomalies in their brain. Instead, their brain could select only one ancestral locomotor pattern available for their locomotion, which was already present since about 400 MYA. This is the ancestral neural network responsible for the diagonal-sequence QL, emerged during the Devonian period of evolution. This gait unstable initially apparently becomes stable with practice during childhood, so that they later move with great ease, speed, and well-developed balance. On the other hand, the locomotor self-organizing process may take a long time in some UTS cases with late emergence of QL at about puberty, see [16,17], a period associated with hormonal changes with beneficial effects on the motor system, accelerating the self-organizing processes, resulting in the emergence of a most suitable locomotor pattern to travel around, walking on all four extremities.

9. UTS vs socio-economic status

Neither the complex systems including the self-organizing processes nor the neuronal group selection mechanisms alone can be realized without considering the dramatic influence of the environmental factors on the holistic processes occurring in the emergence of the UTS. Namely, the single environmental factor shared by all of the cases was their extremely poor living conditions due to their very low socio-economic status. Accordingly, all of the hitherto discovered UTS cases all over the world lived in poverty, resident in developing countries. According to the Databank of the World Bank, the mean GDP (gross domestic product) of the developed countries where no UTS cases were found was 4520.00 US$, whereas the mean GDP of the developing countries where all of the UTS cases were found was 1202.7 US$. The above results suggest that the UTS is a disease of poverty. In other words, UTS with human quadrupedalism and severe mental retardation may be triggered by the environmental factor, low socio-economic status. In this context, the rates of the developmental disorders are almost twice as high in the poorer countries and in the lower income populations than the higher income groups. Over 80% of cases with intellectual disabilities are living in low- and middle-income developing countries [81] Actually there is strong relationship between poverty and common mental disorders, which were found to be about twice as frequent among the poor people compared to rich people [82], where some cases with UTS except Turkey were also found to be resident.

The malnutrition, due to low-income socio-economic status, may cause epigenetic changes, leading to impaired prenatal development of the CNS. A close association between epigenetic status as measured by global DNA methylation and socio-economic status was indeed recently reported [83]; the global DNA hypomethylation was associated with the most deprived group of individuals, compared to the least deprived group [84]. The close relationship between the epigenetic status and the socio-economic status may also be applied to the UTS, a multifactorial-complex disorder, similar to other neuropsychiatric and neurodegenerative diseases. Epigenetics refer to modifications in gene activity without changing the original DNA sequence, depending upon the environmental clues. Similar to other neurodegenerative diseases, the UTS may also comprise multifactorial processes, such as genetic, epigenetic, and environmental components [85] There are consistent reports suggesting the epigenetic mechanisms are responsive to environmental exposures during both pre- and post-natal development in humans. With regard to the most effective environmental factor, the under-nutrition due to low socio-economic status, Heijmans et al [86] reported that persons prenatally exposed to famine showed epigenetic changes compared to their unexposed same-sex siblings. Apparently, these results are consistent with the hypothesis that the triggering factor for the emergence of the UTS with quadrupedalism, mental retardation, and impaired speech may be the under-nutrition, which may detrimentally affect the pre- and postnatal psychomotor development through changing the epigenetic mechanisms.

10. Concluding remarks

The first man habitually walking on all four extremities was discovered nearly a hundred years ago in Turkey by the famous British traveler and writer, Childs, on the Black Sea coast, near Samsun, on the famous Baghdad Road, during the time of Ottoman Empire. After a silent period lasting for almost 100 years, in 2005, 6 cases with habitual quadrupedal locomotion (QL) were described in Southern Turkey. These individuals exhibited a never-before-described syndrome with habitual quadrupedal locomotion, severe mental retardation, and dysarthric speech without conscious experience, mostly cerebello-vermian hypoplasia and mildly simplified cortical gyri, referred to *Uner Tan Syndrome (UTS).* The number of men exceeded the number of women at p =.07 level, suggesting a male preponderance in the UTS. The syndrome showed genetic heterogeneity.

UTS can be considered within the framework of the autosomal recessive cerebellar ataxias, associated with different genetic mutations, such as the disequilibrium syndrome, Cayman ataxia, and Joubert syndrome. These closely related syndromes show overlapping symptoms, such as truncal ataxia, psychomotor delay, and dysarthric speech. These syndromes also show genetic heterogeneity, which is shared by many diseases. Thus, genetics alone cannot be informative for the origins of many syndromes, including the UTS. This is consistent with the dynamical systems theory, with the essential argument there may not be a single element, such as a genetic and/or a neural code, that predetermines the emergence of human quadrupedalism. Rather, the self-organizing processes occurring within a complex system may be involved in the developmental origins of the UTS, consisting of many decentralized and local interactions among neuronal, genetic, epigenetic, and environmental subsystems.

UTS was considered in two subgroups: Type-I and Type-II, the former exhibiting persistent early-onset QL without infantile hypotonia, the latter exhibiting late-onset QL with early-onset hypotonia in skeletal muscles. Comparison with other closely related syndromes such as dysequilibrium syndrome, Cayman ataxia, and Joubert syndrome, suggested that UTS may be differentiated from other similar ataxic syndromes by exhibiting early- or late-onset QL, no hypotonia in skeletal muscles, and no short stature, contrary to severe hypotonia without ambulation, and short stature, among others, in related syndromes, see [16].

Similar to non-human primates, but contrary to non-primate species, the UTS cases utilized the diagonal-sequence quadrupedal locomotion to travel around. The evolutionary advantage of this type of locomotion is obscure. Interestingly, however, only primates with this evolutionarily primary locomotor trait followed an evolutionary route favoring the emergence of higher primates till the human beings. The non-primate mammals with lateral-sequence QL did not follow such a phylogenetic progress. The diagonal-sequence QL was phylogenetically oldest type of locomotion, since the first tetrapods within the Devonian period utilized this kind of locomotion. This suggests that the neural networks for the diagonal-sequence QL were reserved during the evolution from first tetrapods till human beings since about 400 MYA.

A remarkable advantage of the primates with diagonal-sequence QL was that only they could utilize their hands for fine manipulations, freed from weight-bearing functions following erect posture and bipedal walking. The reduced body weight support on hands than feet in non-human primates and human beings with habitual QL (see above) would be beneficial for the development of fine uni- and bi-manual motor skills.

It was suggested that UTS may be considered as a phylogenetic regression in light of Darwinian medicine, associated with an evolutionary understanding of disorders using the principles of evolution, such as natural selection. In some UTS cases, prominent supraorbital tori were observed in cranial MRIs, more or less similar to those in non-human primates. In addition to the diagonal-sequence QL and the body weight support predominantly on the hind limbs more than the forelimbs, this was taken consistent with the theory of evolution in reverse, i.e., the reappearance of a lost function or structure that was typical of remote ancestors.

The developmental emergence of the human QL was related to the self-organizing processes occurring in complex systems, selecting one preferred behavioral state or locomotor trait out of many possible attractors. Since the dynamic systems provide enormous flexibilities in this respect, this is an unpredictable event. With regard to locomotor patterns, the dynamical systems of the developing child may prefer or create some kind of locomotion, resulting from interactions of the internal components and the environmental conditions, without a direct role of any causative factors, such as genetic and/or neural codes. The developmental emergence of human locomotion including QL is a developmental event in which the self-organization processes play the major role, no innate or previously prescribed codes being essential for the emergence of walking during locomotor development. In UTS with impaired balance, the system will find the most suitable and most comfortable, and hence preferred, mode of locomotion, spontaneously generating novel and organized forms and attractor states. These spontaneously occurring unpredictable attractors may result in the emergence of the face-down or face-up diagonal-sequence QL. In light of the dynamical systems theory, the contribution of single factors such as genetic and/or neural codes to the emergence of these locomotor patterns were rejected, considering the current scientific research in these fields, which are consistent with the concept of self-organization, suggesting no single element has causal priority.

The low socio-economic status leading to malnutrition in all UTS cases, all of them being from developing countries, was suggested as a triggering factor for the epigenetic changes occurring during the pre- and post-natal development of the brain. Namely, under-nutrition may trigger epigenetic changes in the brain, affecting the primary variability, in the first phase of locomotor development. In fetuses undergoing to epigenetic changes, the developing brain is then influenced by the aberrant proprioceptive information from fetus, resulting in impaired outcome of the developing brain, associated with psychomotor retardation and selection of the evolutionarily preserved neuronal groups with ancestral locomotor networks, leading a so-called reverse evolution in bipedal locomotion.

With regard to the neuronal group selection theory, the neural system can explore all motor possibilities by means of the self-generated, spontaneous motor activity, and with consequently self-generated afferent information transmission to CNS. The selection of the neuronal groups within the ancestral neural networks in the CNS, available since about 400 MYA, may then lead to the motor development in the next phase, i.e., the neuronal group selection by experience during infancy. In UTS cases, this phase of the locomotor development would stop because of the unavailability of the neuronal groups contributing to the postnatal emergence of bipedal locomotion, continuing ancestral locomotion on all four extremities, resulting from selection of the available ancestral neural networks for QL. So, the infants with UTS cannot select the appropriate neural networks for bipedal locomotion, since some of the neural structures necessary for the well-balanced upright locomotion are damaged in these infants, due to the cerebellar hypoplasia and cortical gyral simplification.

Following the phase of the ancestral neuronal groups responsible for human locomotion, the adaptive variability phase occurs at two to three years of age, with maturation in adolescence through experience. In cases with UTS within the same age range, this adaptive variability phase for bipedal locomotion cannot be accomplished, instead they keep the more primitive motor repertoires from the first variability and neuronal selection phase, resulting in persistence of the selection of the ancestral neuronal groups responsible for the very primitive diagonal-sequence quadrupedal locomotion, evolutionarily conserved since about 400 MYA.

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