Ankylosing spondylitis: Integrated clinical and physiological perspectives

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ABSTRACT

This hypothesis paper draws upon clinical epidemiological and physiological perspectives of axial muscle tone relevant to ankylosing spondylitis (AS). Skeletal muscle tonus is the property of intrinsic tension or resistance to stretch with no additional muscle contraction. The interpretations call attention to novel concepts of the intrinsic axial muscular system contributions to enthesopathic lesions in AS. The axial kinematic chain extends from the entire spine to the posterior aspects of the lower extremities and is essential for postural and mobility functions. Muscles and articular cartilage derive from common embryological precursor cells and are complexly coordinated in the maintenance of postures and dynamic functions. A definitive link between axial muscular dysfunction and respective joint pathology has not yet been demonstrated in AS. However, the following clinical epidemiological and physiological observations raise the possibility of a relationship between axial muscular hypertonicity and AS, which will be reviewed sequentially.

Clinical epidemiological perspectives of AS

The physiopathogenesis of AS remains unknown, despite the strong association with HLA-B27 alleles having been discovered three decades ago (1). The hallmark of AS is radiological evidence of definite sacroiliitis (1), but a probable clinical diagnosis may be based upon defined criteria (2). Although the symptoms of back stiffness and pain in AS usually begin in adolescence or early adulthood, peripheral joint or hip manifestations may antedate back symptoms for a number of years, particularly in juveniles (1). The characteristic pathologic sites of involvement in AS include the sacroiliac joints and entheses, which are sites of attachments of ligaments, tendons or joint capsules to bone within the axial skeleton and at peripheral joints (1, 3). Enthesitis (inflammation at an enthesis) most frequently occurs at sites of greater biomechanical stress (3). It appears that Cosimo de Medici suffered from ankylosing spondylitis (Fig. 1) (4).
minority contributor (circa 20%) to the nearly total genetic (circa 97%) risk of acquiring this disease (9). The major genetic susceptibility (or protective) factors are as yet undiscovered and their physiopathogenetic mechanisms are currently unexplained (8,9). Environmental factors per se cannot be considered the major primary contributors to acquiring the disease (9). Nevertheless, they are hypothesized as being triggers to disease onset in susceptible hosts (1,10). Since the spectrum of AS is so great, separate genetic mechanisms, i.e., severity genes, have been proposed to explain the marked variations in its outcomes (10). Clinical issues and the complexity of testing such dualistic genetic mechanisms, i.e., susceptibility vs severity genes, have been raised (11).

Distinctive clinical-epidemiologic host features of AS (Table I, Fig. 2)
Clinical-epidemiologic host features of AS are distinctive compared to chronic, non-spondyloarthropathy rheumatic diseases, e.g., rheumatoid arthritis (RA) (5,6,12-15, Table I, Fig. 2). The hallmark enthesopathic [i.e., a pathological change at an enthesis] manifestations also differentiate AS (1,3). Such age- and gender-related characteristics suggest biomechanical and musculoskeletal developmental factors as contributors to the diverse risk patterns of this disease (5,11). The onset age of AS is generally young, but its radiological changes typically progress over many years (10). Furthermore, the risk of acquiring this condition markedly decreases in the middle or older ages (Fig. 2). Such incidence patterns are a particular conundrum and may suggest biomechanical tissue failure mechanisms contributing to the onset or course of this disease.

Classical pathological features of AS and their evolving interpretations
A landmark pathology study on AS in 1971 popularized the concept of inflammatory enthesopathy (16). The most striking findings reported were multiple focal microscopic inflammatory lesions localized to ligamentous attachments, i.e., inflammatory enthesopathy. Interpretation of the spinal lesions was based upon 13 necropsy specimens, 12

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**Table I. Differentiating features of ankylosing spondylitis.**

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<td>Genetic factors contribute essentially all risks of developing disease (circa 97%). The strong HLA-B27 association is a minority factor in the total genetic susceptibility risk. Most of the onset risks are contributed by genetically-related host factors, besides HLA-B27. Early axial complaints are often only back stiffness or discomfort. Early increased firmness of lumbar extensor muscles of flexed torso supported on examination table. Later findings in disease progression are limited axial motion and radiographic changes. The male to female ratio increases markedly with the severity of AS (circa 10-fold or more). Males also tend to have more progressive disease than females. Children rarely have back symptoms at onset, particularly girls under the age of 12 years. Adolescents and young adults typically have back symptoms at onset. Onset of disease is uncommon after age 40, and rare after 50 years of age. Incidence and prevalence frequencies of AS correlate with HLA-B27 and colder climates. Lower serum lipid levels in AS patients less than 60 years of age employed in manual labor activities suggest increased energy utilization. Co-occurrence of AS and adolescent idiopathic scoliosis (AIS) is suspected to be rare.</td>
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of which were obtained from 12 to 33 years after the onset of AS (16). The somewhat fragmentary and late nature of the specimens were acknowledged. This author subsequently published a less well circulated review of the articular pathology of AS (17). Mechanisms other than an inflammatory enthesisopathy were indicated as giving rise to the formation of syndesmophytes, which are a ligamentous-related form of an enthesisophyte [i.e., a bony outgrowth (osteophyte) into an enthesis]. The author concluded, "Thus there is a considerable body of evidence from clinical, radiologic, and pathologic sources that these destructive vertebral lesions are essentially due to trauma in a spine which for various reasons is susceptible to stress." (17).

Anatomical studies of the basis for disease localization in seronegative spondyloarthropathy (SpA) at enthesis and related sites have recently provided a better understanding of the pathologic changes that result from compressive and/or shear loading (18). Benjamin & McGonagle (18) emphasize that the enthesis can form part of an "enthesis organ", a collection of tissue specializations adjacent to the enthesis itself, that reduce wear and tear at the latter. One of the components is a thick, fibrocartilaginous periosteum (which they call 'periosteal fibrocartilage') at sites of shear and compression. Greyhounds, bred for speed, have highly stressed bones in their limbs that often fracture as a result of minor trauma. At the insertion of the muscles pathologic changes may occur that can shed light on human diseases (19). Hence, understanding the concept of an enthesis organ may be important in understanding the pattern of bone oedema in the vicinity of entheses in Man (3). However, direct evidence for muscular influences upon loading has not yet been demonstrated as a contributing factor to the bone microdamage observed in human SpA (3,18).

Gender- and aging-maturational influences upon axial muscles: Possible relationships to AS?
Adolescents develop stronger and greater toned muscles at maturation than during childhood, and boys slightly earlier and stronger than girls. The age and gender differences are greater for muscles of the trunk than those of the limbs (20,21). Whereas muscle tone and strength increase in this developmental process, joint flexibility decreases. Spinal manifestations of AS characteristically begin in adolescents and young adults, although peripheral joint manifestations of the seronegative enthesisopathy and arthropathy (SEA) syndrome more often begin in adulthood (22,23). On the contrary, as persons reach middle or older age, muscular strength and tone normally decrease, both in the axial and extremity groups. The incidence of AS (Fig. 2) is consistent with the patterns of increasing peak strength (and tone) in adolescents and younger adults, males more than females, and lessening muscular competence in older ages in both genders.

Clinical observations that suggest axial muscular hypertonicity (axial MHT) in AS
Individual determinants of risk to acquire AS remain mysterious. The disease is relatively uncommon in the general population with HLA-B27, but is significantly greater among such close relatives of proband cases (5,9). Low back stiffness and tightness are characteristic complaints of initially presenting AS patients (24), often without accompanying objective clinical, serological or radiographic findings in milder or early disease. Also, the subsequent course tends to evolve in an individualized manner (25). Preliminary data suggest that AS may be milder in persons with more pronounced joint laxity (26), and that it coexists less frequently than expected with adolescent idiopathic scoliosis (AIS) (27).

Earlier inferences that axial muscular hypertonicity may occur in AS
Based upon clinical-epidemiological observations (Table I, Fig. 2), axial MHT was inferred as a possible contributory factor in AS in 1979 (28). In a subsequent review (5), the concluding section was titled, "Could relative muscle hypertonicity contribute to enthesisopathy in ankylosing spondylitis?"

The stated rationale for this question was, "Such inferences derive from clinical-epidemiologic perspectives, for purposes of generating biologic hypotheses, which may be tested in future research" (5). In fact, biomechanical contributions to enthesitis and osteitis in AS have gained increased attention, as recently reviewed (3,18). However, the underlying physiopathogenesis remains unknown.

Geographical patterns of HLA-B27 and AS: A clue to etiopathogenesis?
The marked geographical variation in population frequencies of AS and HLA-B27 is notable (5, 7, 8), but remains mysterious. In both hemispheres HLA-B27 correlates significantly with colder climates (29). Populations indigenous to severe arctic climates are suspected to have adapted, i.e., by genetic selection, to their harsh environments, rather than to have become physiologically or culturally acclimatized. However, this question is not conclusively answered, despite considerable physiological research (30). In regions of extreme cold and sufficient energy (fat)-rich foods, one may suspect that physiological mechanisms evolved in selected indigenous populations to increase intrinsic energy expenditures in order to preserve core body temperatures (30).

Cold-induced non-shivering thermogenesis (NST) of skeletal muscle has been studied extensively in various animal species (31). Although overfeeding-induced activation of non-exercise activity thermogenesis (NEAT) is not synonymous with NST, marked differences (circa 10-fold) have recently been documented among young adult volunteers living in a temperate climate (32). Males activated NEAT to a greater degree than females. NEAT is the thermogenesis that accompanies activities of daily living, fidgeting, spontaneous muscle contractions, and maintaining posture when not recumbent (32). Such energy balance studies, including the thermic efficiency of exercises of various muscle groups, have not been performed in persons with either HLA-B27 or AS compared to appropriate control subjects.
Preliminary findings of lower serum total cholesterol and triglyceride levels in AS

Increased physical (i.e., muscular) energy expenditures are suspected to be a contributory factor to the observed lower blood lipid levels of manual activity labor workers with AS under age 60 years versus matched control patients, i.e., significantly lower serum total cholesterol (33) and triglyceride (34) levels. The non-smoking AS patients also had higher serum high-density lipoprotein (HDL) cholesterol levels than the other subgroups in this population-based investigation (35).

These preliminary studies need to be repeated in carefully controlled groups of younger, active AS and comparison subjects, before drawing firm interpretations. Loss of weight was a frequent clinical feature of AS in previous generations (36). However, this manifestation is not as evident currently in developed societies where people have more sedentary habits and a greater intake of richer foods than previously. Thermodynamics of the skeletal muscle have been studied seriously in animals (31), but few investigations have been performed in man (37), and none has concerned the axial musculature.

Physiological considerations relevant to axial musculature

Historical perspectives

Studies of biomechanics started with Giovanni Alfonso Borelli (1608-1679), who in 1658 became the Professor of Mathematics at Pisa (38). Luigi Galvani (1737-1798) found that the muscle of a frog contracted when touched by two metals. When two metals, such as iron and copper are in contact, a voltage develops and it was on this that such ‘galvanism’ depends. This was the start of muscle physiology, and indeed the modern era where so much depends on low voltage electrical devices.

Muscle contractions resulting from stimulation have been studied for many years and inevitably animal tissues have usually been used to obtain quantitative data. The more accessible human muscles can also be interesting; in the hand, the adductor pollicis and the first dorsal interosseous have both had extensive study (39). However, there is no such easy path that can be followed to ascertain the properties of muscles of the thoracic and lumbar spine; accordingly other approaches are needed.

Biomechanical considerations

The human thoracic and lumbar spine has only limited movement capabilities and the angular motions possible are small; the main muscle function is postural. A discobolus thrower twists his spine but the rotation at each vertebral segment is small (Fig. 3). Borelli (38) drew parallels between anatomical structures and levers and weights. He noted that muscles act on the limbs with short lever arms whilst the part of the body and the load carried are on much longer lever arms. The tension in the muscles is therefore high compared with the force that can be generated at the end of the limb.

Such considerations apply even more forcibly to the muscles closely associated with the spine. For stability, a very small angular movement at the vertebrae may need to be counteracted by substantial muscular forces generated by the axial musculature close to the bony attachments. If, for instance, an extended arm holds a weight at a distance of 80 cm from the spine, the force produced by the muscles will need to be many times greater. However, the relationship of the abdominal musculature is the converse – a small force generated by the rectus abdominis will have a much increased flexing torque that acts on the vertebral column.

Properties of axial muscles

In the cat, the lumbar back muscles are rapidly contracting, the time to peak of an isometric tetanus being only 29 ms for the longissimus muscles and 34 ms for the multifidi. The spine of the cat is much more flexible than that of man, as can be seen when the animal grooms itself (40, Fig. 4). In running, marked flexions and extensions increase stride length.

Carlson (41) wrote in 1978: ‘While a considerable amount of information is available about the functional organization of mammalian limb muscles, very little attention has been paid to the muscles primarily responsible for movements and posture of the vertebral column.’ This is still the status quo for man.

Muscle fibres are composed of three types: type I are slowly contracting and capable of long-term load bearing, while the others [type IIa and type IIb (or IIX)] are faster acting. Great variability exists in the proportions of fibre...
types between different muscles and in the same muscle between different human subjects. The erector spinae contains predominantly type I fibres, as would be expected from its mainly postural role (20,21). The two main muscles of the lumbar region of the human erector spinae are the multifidus and the longissimus. The multifidus is the shorter deeper muscle and is perhaps principally concerned with stabilization whilst the longissimus may play a more dynamic role. However, no difference in the proportions of fibre types has been found between the two (42).

The power of human paravertebral muscles was studied by Jorgensen (43). The static endurance time is longer than in other muscles and longer in women than in men.

Special properties of the neck
The neck is normally held erect by muscular action and is relatively mobile compared with the rest of the spine. Movements of the head can be recorded comparatively simply, and the electromyographic activity of the nuchal muscles and sternomastoid muscles can be obtained (Fig. 5). The sternomastoid is known to have an unusually high proportion of rapid fibres (44). Interestingly, neck involvement is not usually an early manifestation of AS.

Significance of short range stiffness
Muscles of the human thoracic and lumbar spine will scarcely change their length; the action is virtually isometric, a condition that has long been studied by physiologists. Muscles produce high tension under this condition and even more if, whilst active, they are stretched, although fibres (and possibly their attachments) may then be ruptured. The stiffness of resting muscle cannot be ignored. It has the peculiarity that it is much stiffer for small extensions than for longer ones. There is a ‘short-range elastic component’ which is seen only for changes of up to about 0.2% of the muscle length (45).

In a resting muscle the cross-bridges on the myosin filaments are not entirely inactive, but a very small proportion of them are cross-linked with actin filaments. The links are very stable and have a long ‘life’. The elastic behaviour is due to the flexural rigidity, or spring-like properties, of these bridges. The elasticity is ‘short-range’ because the bridges can be bent or stretched only a small way from the steady-state position before the contacts ‘slip’.

Muscle that scarcely moves has a property called ‘thixotropy’, i.e. it automatically stiffens up; this is related to the ‘short-range elastic component’ (39). The axial musculature is probably operating thixotropically most, if not the entire, time. The stiffening is greatest if the muscle is cool; the use of heat treatments to alleviate muscular discomfort or tightness may depend on these effects.

Challenges of measuring spinal muscle dynamics and tone
Many forms of transport have given rise to extensive whole body vibration. The shaking produced by stage coaches and early railways could be violent and not so long ago some train travel was still uncomfortable (46). Delpech (1777–1832) used whole body motions imparted by a horse-drawn vehicle at a French clinic at Montpellier, evidently in the – surely vain – expectation of a beneficial therapeutic result (47).

Whole body vibration can be induced by the use of tables that tilt or move up and down (Fig. 6) (39). If they can be driven at different frequencies, it will be found that the motion of some parts of the body are greatest at one, and some at another rate. Each segment has a resonant frequency and this is affected by the tone in the musculature; the

Fig. 5. The stability of the head can be investigated by applying rhythmic or other forces through a helmet and a jointed linkage from a torque motor. Resonance is not seen, although commonplace when corresponding observations are made on the limbs. (Reproduced with permission from Walsh E.G.: Muscles, Masses & Motion: The Physiology of Normality, Hypertonicity, Spasticity and Rigidity. London, MacKeith Press, 1992, pg. 156, Fig. 10.36).

Fig. 6. A motor of adjustable speed drove a crank through an eccentric to cause the table to rock. The (now dated) recording system allowed motion of the trunk and head to be recorded. (Reproduced with permission from Walsh E.G.: Muscles, Masses & Motion: The Physiology of Normality, Hypertonicity, Spasticity and Rigidity. London, MacKeith Press, 1992, pg. 179, Fig. 11.13)
stiffer the muscles, the higher the resonant frequency. In a multi-segmented structure such as the body the analysis is complex, but not necessarily impossible so. Naturally, to ascribe the main observable effects to one set of structures such as the axial musculature will depend on an assumption that this is the prime factor, or else on collateral evidence. This is one non-invasive method by which information may be obtainable regarding axial muscle tone. Such a method would allow the progress of a patient to be monitored and could be used to ascertain the effectiveness of a treatment. To restrict the applied forces to the trunk itself involves more substantial engineering.

Intramuscular pressures have been directly recorded from single twitches of the quadriceps femoris (QF) and erector spinae (ES) muscles, using a sterile catheter pressure transducer (Fig. 7) (48). The contractile pressure was considerably higher in the QF than ES muscle of the investigator himself (R.H.), as shown in the illustration. Such an invasive method would not be an optimal manner of measuring comparative axial muscular tone (48). Also, in a single male volunteer, intradiscal pressure was measured in vivo in the nucleus pulposus of a non-degenerated L4-L5 disc over a period of approximately 24 hours (49). A sterile pressure transducer was used and measurements were recorded via a telemetry system. Muscle activity increased the disc pressures, but observable effects to one set of structures such as the axial musculature will depend on an assumption that this is the prime factor, or else on collateral evidence. This is one non-invasive method by which information may be obtainable regarding axial muscle tone. Such a method would allow the progress of a patient to be monitored and could be used to ascertain the effectiveness of a treatment. To restrict the applied forces to the trunk itself involves more substantial engineering.

### Epilogue

The previous concepts of age and gender influences upon axial muscular hypertonicity and its possible role in AS and enthesopathy (5,28) have recently been expanded to include ramifications of energy expenditures (11,33-35). Physiological investigations of axial muscular tone as related to biomechanical contributions to enthesopathy (3, 5, 11, 17,18), as well as their correlations to energy expenditures (32-35), are promising areas for future research in AS and human biology.

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### References

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33. MASI AT, ALDAG JC, MOHAN PC, MURUGAN TSR: Determinants of significantly lower serum total cholesterol levels (TCLs) in ankylosing spondylitis (AS) patients compared to age-, gender-, and medical service-matched control (CN) Pts: Results of multivariate analyses [abstract]. Arthritis Rheum 1999; 42 (Suppl.): S300.


35. MASI AT, MOHAN PC, MURUGAN TSR: Significantly higher serum high-density lipoprotein cholesterol (HDL-C) levels in ankylosing spondylitis (AS) versus control (CN) patients: correlations in the AS patients with non-smoking status (N-SS): low serum triglyceride (TG) levels, and clinical indicators of more advanced axial involvement. Arthritis Rheum 2001; 44: 594.


49. WILKE HJ, NEEF P, CAIMI M, HOOGLAND T, WILKES R H, HILL DK, JONES DA: Neural control of muscle stiffness in response to a novel wrapping compression loading that diminishes local segmental structure and function, e.g., biotensegrity, and to bioengineering aspects of muscle-bone interactions relevant to this hypothesis. Also cited are possible relationships of the axial muscular hypertonicity postulate in AS to evolving concepts of genetic, immunological, and other systemic mechanisms in this disease of unknown causation. The upright spine of bipeds is considered to be one of the greatest evolutions in the human lineage (50). Principles of "bio-tensegrity" have recently been proposed as an alternative biomechanical model of the spine, in contrast to the classical "tower of blocks" (50, 51).

The model applies the tensegrity principle (e.g., geodesic-dome geometry) of R. Buckminster Fuller (52) to the spine and other organ systems (50, 51). Tensegrity (a contraction of "tensional integrity") is an architectural system that stabilizes itself mechanically by balancing counteracting forces of compression and tension (52). Structures are viewed primarily as continuous networks of tensional elements (e.g., muscle fibers and ligaments) and secondarily as incorporating local islands of compressional loading (e.g., vertebrae of the bony spinal column). This model accounts not only for the great stability of the normal muscular spinal system, but also its low energy mechanics, flexibility, mobility, and far greater strength than is permissible with an architectural column (51, 53). The tensional elements of the spine and body (i.e., the soft tissues-muscles, fascia, ligaments, and connective tissues) have an integral role in stabilizing the spine (51, 53-56). For example, the intrinsic tonus of axial muscles is normally sufficient to maintain posture in quiet, exactly balanced standing (i.e., static equilibrium), without surface EMG-detectable activation-contractions (51). Even though Leonardo da Vinci hypothesized that muscles stabilize the spine like the guy ropes of a ship's mast (57), muscles have largely been ignored as structural members, in contrast to their specific motor functions (51). Axial muscles may also stiffen the spine by contributing to a novel wrapping compression loading that diminishes local segmental

Addendum: Future research considerations A.T. MASI

In this section, attention is called to recent biomechanical concepts of spinal
tal shear forces and tissue stresses (58). The multimuscular-osteoigamentous spine system is profoundly complex. Recent research indicates that disorders or dysnergies of muscle function can adversely influence loading on associated bones and attachment sites. Compressive forces or tensional stresses that exceed tissue tolerances can cause tissue damage, as may occur in the enthesopathy lesions of AS (3, 5, 11, 17, 18). Direct validation of tissue loads on the spine is hardly feasible in humans (56). However, mathematical modeling can estimate the components of spinal muscle properties related to its complex functions, e.g., its intrinsic stiffness, actively generated forces (i.e., EMG-detectable contractions), and its stored contractile energy (55, 56). At low forces, muscle stiffness is a substantial contributor to spinal stability (55, 56).

The biodynamics of impact loading on the lower extremities has been studied during running (59). Heel strike initiated shock waves were increased in fatigued subjects, which implies a decreased capacity of fatigued muscles to attenuate and dissipate such shock waves in a normal fashion (59). Also, the degree of bone strain in the human tibia is correlated with muscular function (60). The strain rate was increased after fatigue, with a greater increase in younger as opposed to older persons (60). Possibly, younger runners may have had greater impacting forces?

In AS, lower extremity arthritis predominates, particularly in juveniles presenting with tarsitis and enthesopathy in the SEA syndrome (22). Biomechanical and gait analyses studies promise to enhance our understanding of AS and the SEA syndrome (11).

A “proof of concept” of the proposed hypothesis cannot be easily tested by controlled experiments at this time. Nevertheless, its parameters can be further investigated and integrated with results from other avenues of research in AS. Pathogenetic mechanisms of AS and their implications for therapy are being actively pursued (61). In particular, genetic studies are rapidly evolving (62). For example, the best fitting susceptibility model studied was a five-locus multiplicative interaction between loci (63). Such an oligogenic multiplicative model is consistent with the results of independent mathematical analyses of single-year cumulative frequency distribution models of onset ages in primary AS (64). In such risk models (63, 64), factors that influence axial muscular “passive stiffness” or tonicity, such as physical maturation polymorphisms and gender, could possibly be some of the suspected oligogenic host components that determine susceptibility or onset patterns of AS. Regarding immunological research, tumor necrosis factor alpha (TNFα) is postulated to play a central role in development of the sacroiliitis of AS (65). However, TNFα production by peripheral T cells in AS patients was found to be significantly lower than in normal subjects (66). Like the contrasting incidence rates of AS (Fig. 2), this immunological result is opposite to findings in RA (66, 67). TNFα is mainly produced by monocytes and macrophages, and to only a lesser degree by T cells (66, 67). Local activation of TNFα in the sacroiliac (SI) joints may reflect primarily innate, rather than adaptive, immunological pathways (67). Perhaps, SI joints may have chronic tissue stress overloading in AS from axial muscular hypertonicity? One might suspect that increased tissue microinjury could activate TNFα and become one of several physiopathogenetic determinants in AS. Prospective studies will be needed to determine the sequential relationships between axial muscular tonicity status vis-à-vis immunological activation in the sacroiliitis of AS. In conclusion, this commentary proposes novel host pathways in the complex multifactorial causation of AS. The hypothesis of axial MHT is still necessarily simplified at this stage, and is offered to stimulate critical, controlled, physiopathogenetic investigations in this challenging disease.

References
52. FULLER RB, LOBH AL: Synergetics; Explorations in the Geometry of Thinking. NY, Macmillan Publishing Company, 1975; 314-431.