Gait analysis and cerebral volumes in Down’s syndrome

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ведение cerebral volumes computed using a voxel-based morphometry algorithm and walking patterns in individuals with Down’s syndrome (DS), in order to investigate the origin of the motor problems in these subjects with a view to developing appropriate rehabilitation programmes.

Nine children with DS underwent a gait analysis (GA) protocol that used a 3D motion analysis system, force plates and a video system, and magnetic resonance imaging (MRI). Analysis of GA graphs allowed a series of parameters to be defined and computed in order to quantify gait patterns. By combining some of the parameters it was possible to obtain a 3D description of gait in terms of distance from normal values. Finally, the results of cerebral volume analysis were compared with the gait patterns found.

A strong relationship emerged between cerebellar vermis volume reduction and quality of gait and also between grey matter volume reduction of some cerebral areas and asymmetrical gait.

An evaluation of high-level motor deficits, reflected in a lack or partial lack of proximal functions, is important in order to define a correct rehabilitation programme.

KEY WORDS: cerebral volumes, Down’s syndrome, gait analysis, optimised voxel-based morphometry

Introduction

It has been pointed out that the delayed and patchy development of skills in different domains observed in

Down’s syndrome (DS) is consistent with neuroscientific evidence of atypical brain structure and organization in this condition (1). Indeed, new neuroimaging techniques are able to show a complex pattern of cerebral structural changes in DS, while magnetic resonance imaging (MRI) studies show that individuals with DS typically have a smaller overall brain volume, with significant reductions recorded in both cerebrum and cerebellum volume (2-4). There is also neuropathological evidence that these differences in brain structure are not present in utero but emerge during early development in the context of retarded growth patterns (5). Delayed myelination of neurons in the central nervous system (CNS) is part of this picture of early neural developmental delay. Myelination corresponding to an age of 9-11 months was observed on MRI scans in an 18-month-old child with DS, and the authors remarked that the degree of myelination delay correlated well with the observed cognitive delay (6). The point has also been made (1) that this delay in cortical myelination implicates transcortical pathways and might underlie the atypical pattern of acquisition of motor milestones in DS. Other white matter abnormalities reported in individuals with DS include a narrower corpus callosum, which may affect the transfer of semantic information across hemispheres (7). These alterations in cortical volume and pathways may also underlie the model of atypical cerebral organisation of language and motor skills described in DS (8-11). As remarked elsewhere (1), this model “proposes that while left-hemisphere specialization for organization and control of sequential motor response is similar in DS and in non-disabled adults, there appears to be an atypical left-ear/right-hemisphere advantage for the perception of speech sounds in DS”. One study describes a discrepancy between motor performance in response to verbal instruction as opposed to visual demonstration (12). These findings have important implications for motor skill acquisition and strategies of educational intervention in DS.

A key feature of brain structure in DS is the multifocal pattern of the neural deficits (4), which is consistent with the patchy skill development described in the developmental literature. Several studies have reported localised volume reduction in areas including the frontal cortex, limbic areas and cerebellum, significant right-left cerebral asymmetries in the limbic region and a larger parahippocampal gyrus (4,5,13). A neurobehavioural study reported abnormal event-related potential responses recorded over the frontal cortex in children with DS consistent with frontal-attentional processing of visual tasks (14). Similarly, an atypical hippocampal volume was consistent with slowed speed of orienting to and categorising of auditory information, and impairments in immediate auditory memory (15).
In view of the documented “clumsy” movement of DS subjects, and considering that the literature contains no descriptions of relationships between MRI and functional limitations in gait, the aim of the authors was to make a first attempt to study in a quantitative manner the relationship between brain abnormalities and their reflection in functional limitations at the level of the effectors.

Materials and methods

Nine children with DS, all subjects whose clinical picture suggested a possible malformation of the atlanto-occipital joint, were submitted to MRI acquisition. We also recruited 10 control subjects, of the same age as the DS subjects, mainly from among healthy children and adolescents referred to our department for general clinical examination. All the controls were right-handed and all were screened for neurological impairments and for any history of learning disability or developmental delay. Potential participants were excluded if they presented with untreated medical conditions that might affect cognition (e.g., hypothyroidism in DS), or with a history of severe head trauma requiring medical attention. In all the subjects with DS, the diagnosis was confirmed by karyotype examination that showed trisomy of chromosome 21. The protocol was explained to all the subjects and their parents and written informed consent was obtained from the parents. The study had local ethics committee approval.

High-resolution contiguous axial T1-weighted MRIs were acquired at the Radiology Department of the IRCCS San Raffaele Pisana–Tosinvest Säntis institute in Rome, using a 1.5 Tesla Philips Intera scanner (Philips Medical Raffaele Pisana–Tosinvest Sanità institute in Rome, us-

The optimised-modulated VBM protocol comprised the creation of customised GM, WM, and CSF templates, as reported in many works in the literature (23,24): the GA, which is an efficient tool in gait pattern description and sex of each subject were considered nuisance co-

Statistical inferences were made voxel by voxel using an analysis of covariance design, in which the TIV, age, and sex of each subject were considered nuisance co-

The remaining voxels were modulated, multiplying them by the Jacobian determinants derived from the spatial normalisation step, in order to account global differences in head size, integrating the voxel values across each subject’s modulated GM, WM, and CSF partitions, with non-brain voxels removed using a series of morphological operators (erosions and dilations). Standard unpaired t-tests were first used to compare TIVs between the DS subjects and the control group. The imaging data were then analysed to determine regional brain volume differences. Regional (voxel-based) differences in GM, WM, and CSF volume across the whole brain and between groups were assessed using the theory of Gaussian fields (16,22) and carried out using the general linear model, as implemented in SPM2. Statistical inferences were made voxel by voxel using an analysis of covariance design, in which the TIV, age, and sex of each subject were considered nuisance covariates. Voxels with an intensity of less than 0.05 were excluded from the statistical comparison.

The same nine children with DS were also submitted to a first attempt to study in a quantitative manner the relationship between brain abnormalities and their reflection in functional limitations at the level of the effectors.
equipment was composed of 12 optoelectronic cameras (Elite, BTS, Italy), two force plates (Kistler, CH) and two video systems (VideoController, BTS, Italy). The GA was conducted placing markers on the subject’s body according to the Davis protocol (25).

The subjects (children with DS and controls) were asked to walk barefoot at their self-selected speed along a 10-metre walkway containing the force plates. The subjects were asked to start from a pre-defined point, which allowed them to put only one foot on each plate. In order to guarantee the consistency of the results, each subject performed several trials.

In order to quantify gait patterns, punctual gait parameters were computed and plotted on GA graphs.

Relationship between gait analysis and magnetic resonance images

Since MRI is not routinely performed in subjects with DS, we had at our disposal, for this study, MRI data from only nine children with DS, who, as mentioned, were also submitted to gait analysis.

There are many variables to consider when comparing one walking pattern with another. The literature (24) proposes, for some pathologies, synthetic indices to allow easy and fast evaluation of motor characteristics; to date no such index has been proposed for the characterisation of the DS population. A synthetic index, derived from a set of appropriate gait parameters, is a numerical value that is able to provide global information about the quality of gait. In order to classify the gait of DS children, which can range from less to more functional, and since the current literature does not offer synthetic indices for DS subjects, this work was conducted in an attempt to assemble gait parameters and to order, from less to more functional gait, the data obtained from the children with DS analysed. We defined sets made up of three punctual parameters calculated from the GA graphs; these were then represented in a 3D space to detect the differences between patient and normative data, computing the spatial distances. In each plot, mean values and standard deviations of normative data were represented as, respectively, the centre and axis of an ellipse. The following formula was used:

\[
\frac{(x - x_c)^2}{a^2} + \frac{(y - y_c)^2}{b^2} + \frac{(z - z_c)^2}{c^2} = 1
\]

in which \(a\), \(b\) and \(c\) are standard deviations of the parameters drawn on the \(x\), \(y\) and \(z\) axes respectively, and \(x_c\), \(y_c\) and \(z_c\) are the coordinates of the ellipse centre, that is the mean values. In order to compare data from two of the children with DS (the one with the most and the one with the least functional gait), we first built the ellipse of the normative data: the mean of the ten controls was taken as the centre of the ellipse, while the standard deviations of the control group defined its axis.

Hip-Knee-Ankle kinematic chain (HKA chain). In order to evaluate the HKA chain in the sagittal plane, the angles at initial contact (AICs) of hip, knee and ankle were considered and the relative values plotted.

Hip kinematics and kinetics. The hip joint is controlled by flexor muscles during the extension in stance phase: in the relative plot, maximum extension angle in the stance phase, maximum flexor moment and work generated at the hip are represented.

Other spatiotemporal input parameters involving the knee and ankle joint were also computed. In this paper, however, we focus on the two sets presented above. In order to characterise 3D graphs, parameters of distance from normative data were computed for the right and left lower limbs of the DS subjects, i.e., the 3D distance between the control group index and the index for the single DS patient, for the right and left sides (respectively, DIST N-R3D and DIST N-L3D), in which \(x_{CG}\), \(y_{CG}\) and \(z_{CG}\) are the coordinates of the control group, while \(x_{DS}\), \(y_{DS}\) and \(z_{DS}\) are those of the DS subjects. In this way we were able to establish which of the two children considered had the least functional and which had the most functional gait and finally to make a comparison with VBM data.

Results

A number of authors, in discussing motor problems in DS, refer to Crome and Weller (26) who reported a reduced total brain weight in children with DS (on average 76% of the normal weight), and in particular a smaller brainstem and cerebellum (66%). The cerebellum, which receives information from the vestibular system and the motor apparatus, plays an important role in the coordination of posture and movement. When disturbances occur in the cerebellum, it is possible to observe irregularities in balance and coordination of movement, for example, and hypotonia. Facilitation of gamma motor neurons is regulated at brainstem level and activation of alpha motor neurons via the gamma loop is essential for the maintenance of posture, because the extensors involved must, through this system, have enough tonus at their disposal. The connection between these neuroanatomical abnormalities and the movement disturbances shown by individuals with DS, while seemingly obvious, has yet to be demonstrated. We thus conducted a pilot study compare GA and VBM results.

Results of gait analysis: from more to less functional gait

Walking in the children with DS was classified by evaluating their GA reports, using the indices of distance described earlier. The indices considered the global situation of the lower limbs for each subject and showed that the subject with the best motor strategy could have a worse punctual index than a subject with the least functional gait. In this way, we defined the gait of the children with DS: S1 was found to have the most functional and S2 the least functional gait.

S1. In the sagittal plane, S1 showed a pelvic tilt close to normal values; the hip was in a mildly flexed position throughout the gait cycle, but the range of motion (ROM) was quite similar to that recorded in the control group. The knee joint, during the stance phase, was slightly flexed, but the maximum angle during swing was close to normal.

Ankle dorsiplantarflexion, during the gait cycle, showed...
decreasing ROM, a typical feature in the DS population, and an extrarotated foot progression.

As regards the kinetic data, S1 showed normal dorsi-plantarflexion moment peak values during terminal stance; the power generated at this level, even though it was lower than the values recorded in the control group, was the highest recorded in any of the DS subjects considered in this analysis.

S2. This subject was found to show the least functional gait, recording the highest anterior position of the pelvis. This was due to a more flexed hip, which, moreover, showed a limited ROM. The knee joint revealed a worse condition in terms of ROM than S1. The ankle joint showed a prolonged plantarflexion. Kinetic data underlined a decrease in the dorsi-plantarflexion moment peak and the lowest value of ankle generated power in the DS population.

The differences between S1 and S2 were also confirmed by the 3D distance indices.

Considering the HKA kinematic chain (Fig.1), which included the AICs of the hip, knee and ankle, the 3D distance between the S1 value and the normal values was less than that found between S2 and the control group: 17.28 (DIST N-R3D = 16.38; DIST N-L3D= 18.24) in S1, versus 43.32 (DIST N-R3D = 50.51; DIST N-L3D= 34.13) in S2.

Focusing on the hip joint (Fig. 2), we also noticed that S2 gave greater 3D distance values than S1; S1 also showed better values than S2 at knee level, the two subjects recording, respectively, 3D distance values of 21.31 (DIST N-R3D = 21.73; DIST N-L3D= 20.9) and 26.91 (DIST N-R3D = 20.43; DIST N-L3D= 33.4). As regards the ankle results, S1 again showed values less distant from normality than those of S2.

Figure 1 - HKA chain 3D graph for S1 (blue square and red cross) and S2 (blue triangle and orange square). The green ellipse represents the control group.

Figure 2 - Hip indices 3D graph for S1 (blue square and red cross) and S2 (blue triangle and orange square). The green ellipse represents the control group. (HM mins = Hip moment minimum in sagittal plane; HmSts = minimum hip angle in stance phase).
Relationship with cerebral volumes

Following the characterisation and the classification of gait in the DS subjects, the relationship with cerebral volume was considered, using data obtained at the IRCCS San Raffaele Pisana institute, in Rome. Cerebral volume survey with VBM provided information not appreciable on MRI alone, which in most patients gave negative results. We considered, in the first analysis, the cerebral volumes of S1 and S2: S1 (Fig. 3) showed, mainly, a GM volume reduction in the cerebellum, with higher impairment on the left side, and no cerebellar vermis abnormalities; S2 (Fig. 4) also showed GM volume reduction in the cerebellum, with a symmetrical pattern, but in this subject there was cerebellar vermis involvement. These data were indicative of more functional motor control in S1 than S2, a hypothesis confirmed by the GA results described above.

The two subjects with DS whose GA classification was analysed in this study showed parallelism of VBM results: a more functional gait was associated with a lower cerebral volume reduction. In particular, a relationship between gait quality and cerebellar vermis impairment was observed: indeed, impairment of this cerebral structure was found to be the element best able to discriminate gait performance. The cerebellar vermis plays an important role in trunk and lower limb motion coordination and lesions at this level lead to postural and motor alterations.

Discussion

Motor disability is widespread among individuals with DS. It includes longer motion and reaction times, balance and postural deficits, and co-contraction of agonist and antagonist muscles. These deficits may be causally linked to delays in reaching motor development milestones. The motor dysfunction in individuals with DS involves impaired muscle control, leading to what parents and health professionals often call “clumsiness”. The neuropathological basis for motor dysfunction in DS is unknown, but cerebellar dysfunction, delayed myelination, as well as proprioceptive and vestibular deficits have been suggested as possible causes. The delay in motor development in DS is linked to the generalised muscle hypotonia and ligament laxity that is characteristic of the condition.

In this study we identified, through examination of GA indices, anomalies in gait pattern that showed strong similarities with the results presented in other studies on movement in Down’s syndrome. We also noticed in our results a high standard deviation among analysed DS children in terms of overall gait pattern: some children presented a more functional gait than others, which resulted in less clumsy movement. The literature also reports that individuals with DS present different neurological profiles, with some subjects showing a better neurological performance. Although much research has been done into this topic, studies on the motor classification of DS subjects and the evolution, from a neurological perspective, of their functional limitations, examined by clinical neurological tests and MRI, are lacking.

This study, prompted by clinical needs, set out to establish the opportuneness of exploring in depth the global features of DS and its consequences at the level of the motor control system: for these reasons, an evaluation of high-level motor deficits, reflected in a lack or partial lack of proximal functions, is important in order to define correct rehabilitation programmes.

Often, the decision making in the organisation of a rehabilitation programme is a multidisciplinary process which also involves gait analysis. Gait is normally interpreted through comparison of a patient’s trend with the normative band and the rehabilitation programme generally aims to bring the patient’s parameters back within normal range. However, it has to be appreciated that the residual motor capacities of a pathological subject do give him or her the possibility of achieving a functional level comparable with that of a healthy subject. In view of these considerations, and in order to create a useful and correct rehabilitation programme, it can be suggested that the features of movement of individuals persons with DS should not be considered “wrong” or “pathological”, as they could well be consequences of adaptive processes within the CNS, which is “aware” of its power and limitations and tries to optimise motor performance in functionally important tasks (1).
This study highlights the need to understand in depth the origin of motor control anomalies in DS in order to identify at the level at which to target the rehabilitation programme. In fact, in order to establish meaningful re-habilitation goals, all those involved in the rehabilitation planning need to know what physical rehabilitation can realistically achieve and how: some problems are related to orthopaedic limitations, others to cognitive impairments. For this reason, it is very important that physical rehabilitation be performed in tandem with cognitive re-habilitation.

Future studies should present other methods of analysis, focusing on the registration of differences in gait patterns using different approaches, such as the polynomial function (27), which might allow better gait classification of the DS population.

References