Down syndrome presenting with multiple sclerosis, thyroid dysfunction, and diabetes mellitus

Multiple autoimmune disorders in a genetic disorder

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ABSTRACT

تعد متلازمة داون من الأمراض الكروموسومية الشائعة التي يمكن التعايش معها، كما يُعرف ارتباطها بالعديد من الأمراض المناعية الذاتية. ويعد التصلب العصبي المتعدد الذي يصيب الجهاز العصبي المركزي من الأمراض الالتهابية المزمنة المزيلة للنخاعين. لقد تطرق الأدب الطبي إلى وجود العلاقة بين متلازمة داون وأمراض المناعة الذاتية سابقاً، ونحن نستعرض في هذا المقال حالة مريض يعاني من متلازمة داون مع الأمراض التالية: التصلب العصبي المتعدد، وداء السكري، واضطراب الغدة الدرقية. لقد أظهرنا في هذا المقال مدى انتشار التصلب العصبي المتعدد بين مرضى متلازمة داون مثله مثل أمراض المناعة الذاتية الأخرى.

Down syndrome (DS) is one of the most common survivable chromosomal disorders, and is well known to be associated with multiple autoimmune diseases. Multiple sclerosis (MS) is a chronic inflammatory autoimmune demyelinating disease of the central nervous system. An association of DS and other autoimmune disease has been previously reported, and we report one case of DS in coexistence with MS, diabetes mellitus, and thyroid diseases. We suggest that MS, such as other autoimmune diseases, is prevalent in DS patients.

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Down syndrome (DS) is the best known of the chromosomal dysgenesis syndromes. The frequency is one in 1000 births, and this condition accounts for approximately 10% of all reported series of cases of severe mental retardation.[1] Associations of DS and autoimmune diseases have been already reported. The autoimmune disease may affect both the endocrine system (thyroid, pancreatic islets, and adrenal gland), and the non-endocrine tissue (psoriasis, and inflammatory bowel disease).[2] Down syndrome co-exists with an increased incidence of autoimmune thyroiditis, primary sclerosing cholangitis, systemic lupus erythematosus, insulin-dependent diabetes mellitus, celiac disease, and alopecia areata.[3] Autoimmune thyroid disease (AITD) is the most frequent autoimmune disorder coexisting with DS. Among 2 major clinical outcomes of AITD, Graves' disease and Hashimoto's thyroiditis (HT), HT most often accompanies DS. Insulin-dependent diabetes mellitus (IDDM) occurs in 1.4-10.6% of individuals with DS, which is significantly higher than in the general population. Furthermore, age at diabetes onset in DS infants is earlier compared with non-trisomic children. In addition, the portion of children with IDDM diagnosed within the first 2 years of life is markedly higher among the DS population (22%) compared to that in the general population.[3] Multiple sclerosis (MS) is an autoimmune disease, which is characterized by demyelination, axonal, and neuronal degeneration. There are limited reports in the literature of cases of DS associated with MS. We describe a young DS patient with hypothyroidism and diabetes mellitus associated with MS who experienced sudden onset limb weakness. Our objective in presenting this particular case is to highlight the association of MS in Down syndrome patients.

Case Report. A 21-year-old woman, with no family history of MS, was referred to our clinic for evaluation of neurological symptoms. One year earlier, her mother noticed a sudden weakness of the left leg with difficulty

in walking, and 3 days after that she also noted left arm weakness in the patient. She is the second child of a mother who was 34-years-old at the time of delivery. Mental deficiency was noted when she was a baby, and she also suffered from an incomplete acquisition of language. Down syndrome was confirmed by evaluation and chromosomal study. On follow up workup at that time, laboratory data showed the presence of IDDM and hypothyroidism, and she was treated accordingly. They initially ignored the neurological symptoms as the first neurological symptom resolved spontaneously, however, the new symptoms recurred 2 months prior to their attendance at the clinic, when she presented with an obvious inability to walk. On physical examination, archetypal features of Mongolian were seen (round head, open mouth, stubby hand, slanting of palpebral fissure, short stature) imparting an unmistakable picture. Chromosomal analysis was performed 2 times, and mosaic pattern and chromosomal dislocation were ruled out. On neurological exam she had left sided body weakness with motor force of 3/5, and mild hypotonia in all other extremities. Deep tendon reflexes were increased, and Babinski sign was positive on the left. Cranial nerves were normal, and eye movement was intact, except end point nystagmus on both sides. Overall Expanded Disability Status Scale (EDSS) was 4-4.5. Brain MRI showed multiple high signals on T2W, and one Gad-enhancing lesion in the periventricular white matter and cerebellum (**Figures 1 & 2**). Cervical MRI showed only one high signal T2 intensity at the C2-4 level. Analysis of CSF was not performed as her parents were not comfortable with her undergoing lumbar puncture. Routine laboratory tests were normal. Laboratory tests for celiac disease were requested as well as antinuclear, antimicrosomal, and anti DNA antibody, cytoplasmic and perinuclear antineutrophil cytoplasmic, VDRL, and anti toxoplasmosis antibodies, which all were negative. Thyroid function tests (TFTs) showed abnormalities due to her history, and this was also true for blood sugar tests (T4: 3.1 [4-12], TSH: 0.06 [1.6-5.6]), fasting blood sugar: 154 (85-104), HbA1c: 7.9 [<6], antithyroglobulin Ab: positive). She was diagnosed as definite relapsing MS and subsequently treated with high dose steroids for 5 days. After one month the weakness completely resolved, and beta-interferon was started weekly for prevention of relapses. She was doing well without any further relapse or progression at the time of this report.

Discussion. This is the third documented DS conjunct with MS associated with 2 other (IDDM and hypothyroidism) autoimmune diorders.[4,5] Only one other case with DS has been described in association with another demyelinating disease, neuro myelitis optica (NMO).[6] Only one other case of DS associated with 3 autoimmune diseases (hypothyroidism, DM, and celiac disease) has been reported.[7]

Autoimmune thyroid disease is the most frequent autoimmune disorder co-existent with DS, and approximately 30% develop thyroid disorder. The onset of the disorder is usually insidious. Most patients have a euthyroid goiter, or goiter with mild hypothyroidism with growth retardation. Most of the affected patients display detectable circulating thyroid specific autoantibody.[1] The link of the pathogenetic relationship between DS and MS remains unclear. It may be coincidence, or due to an impaired immune response. Known factors suggesting immune dysregulation in DS include: abnormal development/morphology with diminished cortex, enlarged Hassall corpuscles, altered lymphocyte sub population in peripheral blood and thymus with evidence of T-cell activation, premature aging effects, increased susceptibility to infection, and increased risk of malignancy. There are 2 ways in which genetic

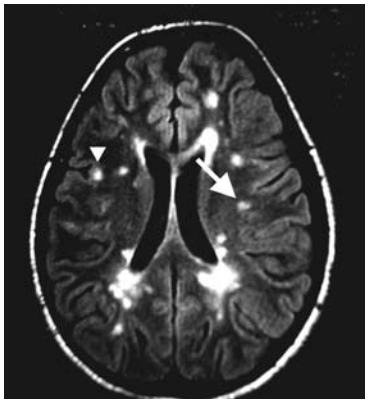

Figure 1 - The axial view of brain MRI (FLAIR) showing the multiple high signal lesions in the paraventricular (long arrow) and juxtacortical area (arrowhead).

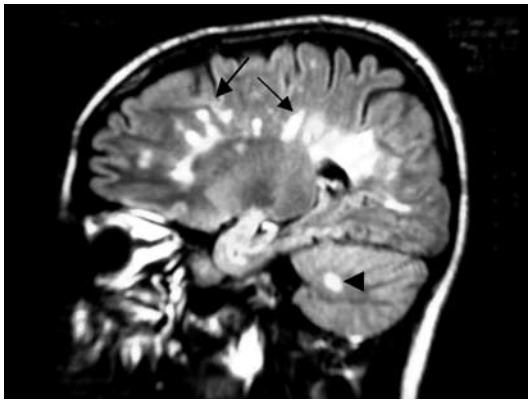

Figure 2 - Sagittal view of brain MRI (FLAIR) showing multiple bright lesions in the corpus callosum (arrows) and one lesion in the cerebellum (arrowheads).

susceptibility to autoimmune disease is conferred in DS.[8]

There are several immune abnormalities in DS patients. Low rate production of cytokines such as interleukin-2 and some other cytokines and also B cell abnormalities accompany DS. These abnormalities may account for the predisposition to autoimmune disorders.[8] A biased CD4+/CD8+ lymphocyte ratio was observed in DS patients. Reduction of helper/inducer CD4+ ratio, and increased numbers of suppressor/cytotoxic (CD8+) cells were seen.[9] These changes are nonspecific and are seen in other autoimmune disease.

Weilbach and Toyka[10] estimated the expected co prevalence calculation based on population and prevalence data of DS and MS. The expected manifestation of both diseases was significantly higher than one MS case, which suggests a 'protective' effect of DS in MS. Candidate genes for protective immunomodulation might include interferon receptor I and II and S100b (calcium binding protein b-subunit).

According to a Medline search, there are limited reports of DS conjunct with MS in the Middle East. This is the third case of DS associated with MS who has been reported after one from Western Europe and South America. The incidence of MS in these counties is lower than Europe. Epidemiologic data make less likely the hypothesis of the protective effect of DS against MS, which was introduced by Weilbach and co-workers.[10]

In conclusion, we suggest that MS, as with other autoimmune diseases, might be more prevalent in DS patients, and so we recommend neurological and other diagnostic tests in all patients with DS presenting with neurological symptoms or complaints, even vague and non specific.

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