The Silver Syndrome and the Man behind the Syndrome: A Tribute to J.R. Silver 1931–2021

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Familial spastic paraparesis is a non-progressive disorder. However, clinical experience shows that after trauma, disease, surgery, or limb fracture that force a patient's long immobilization, a significant functional deterioration is observed. I describe two patients with Silver syndrome who experienced such functional deterioration after sustaining a simple fracture. A description of Silver syndrome and a biographical sketch of Dr. Silver, who explained the disorder in 1966, are given.

PATIENT DESCRIPTION

CASE 1

The patient was born in 1947 in Kochin, India. Her parents are cousins. In 1950 the family immigrated to Israel. Of five children, three were diagnosed as having familial spastic paraplegia. In 1962 the patient was hospitalized due to exaggerated lumbar lordosis, spastic paraparesis, and in both eyes fundi examination showed some pathological findings. Years later, she reported that despite of her marked disability, she married an able-body man, and they had three children. She experienced an active life as a mother and a housewife. She refused to undergo any further genetic consultation.

Until her fall, she walked aided only with canes. On 18 February 2006, she fell and sustained a subcapital left femoral fracture, which was surgically stabilized. She was referred to our rehabilitation medicine ward. She presented with essential hypertension. She was alert and eager to return to her former functional status. Neurologically, she had spastic paraparesis with bilateral interossei atrophy. Although she tried to return to active walking, she was unable to stand unaided and to walk. Most probably, the new insult (a fall, bone fracture, surgery, and secondary immobilization) deteriorated her functional status. Weakness in her upper limbs as well as chronic paraparesis made standing and walking an unachievable goal. Confinement to a wheelchair was inevitable and proper rehabilitation treatments helped her to adapt her to new situation and to accomplish some independence in activities of daily living (ADL).

CASE 2

A 24-year-old Arab woman, presented with familial spastic paraplegia with some weakness in her hands and severe pigmentation over her face and cervical region. One of her sisters presented with the same genetic variant.

Our patient reported frequently falling while walking. She was referred to our outpatient clinic because of new functional loss after sustaining a right malleolar fracture, which was treated with a plaster of Paris cast. Although she received extensive physiotherapy, her limp worsened, and she needed new walking aids. She finished a course to become a medical secretary and gained full independence in all ADLs.

COMMENT

Silver syndrome [1] is also known as spastic paraplegia with amyotrophy of hands and feet, or as Silver spastic paraplegia syndrome. In 1966, Silver [2,3] reported on two families with spastic paraplegia with amyotrophy of the hands inherited in an autosomal dominant pattern. In the larger family with more affected members, age at onset of gait abnormalities was 8 to 40 years and for hand involvement 14 to 60 years. Both lower limb spasticity and amyotrophy of intrinsic hand muscles were present in most affected individuals. All had weakness of intrinsic hand muscles, with severe amyotrophy, most marked in the thenar eminence. There was also mild impairment of vibration sense in the lower limbs of older individuals [1].

The genetic mapping was identified as gene locus 11q13, 11q12-q14 [4]. The hereditary spastic paraplegias are a clinically variable and genetically heterogeneous group of disorders characterized by progressive and lower limb spasticity and weakness. Silver syndrome is a particularly disabling autosomal dominant form of the disease in which there is associated wasting of the hand muscles. Because genes for hereditary spastic paraplegia can produce highly variable phenotypes, the eight known autosomal dominant loci were investigated for linkage to Silver syndrome. Genotyping of these loci in two large multigenerational families was incompatible with linkage to any of these regions, suggesting that an additional locus is responsible for this syndrome.

THE MAN BEHIND THE SYNDROME: J.R. SILVER (1931–2021)

John Russell Silver was born in 1931 to a Jewish family in London, England. He finished his medical studies in 1954. In 1957 he worked for a year as a registrar for Sir Ludwig Guttmann at the National Spinal Cord Injury Center, Stoke Mandeville Hospital, England. After completing his National Service (orthopedic section, RAF), he continued his training at Middlesex Hospital, London. He returned to work with Sir Ludwig and later was appointed consultant-in-charge of the spinal center in Liverpool. In 1970 he returned to Stoke Mandeville Hospital and worked there until his retirement in 1993.

He published more than 100 articles, mainly on spinal cord injuries but also on various aspects of the history of medicine. His impressive study on the history of the treatment of spinal injuries, which was based on his MD thesis, was published [5].

CONCLUSIONS

New significant functional deterioration among people with chronic stable disability even after simple trauma or disease is not found in the literature. Despite the non-progressive nature of the original disability, new onset immobilization (after a disease or trauma) often leads to new functional losses. People who are in a vulnerable state of brittle equilibrium can be easily shaken by new stressors. These case reports illustrate the interplay between biological, psychological, and therapeutic factors that are affected by the aging process.

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Good fiction creates empathy. A novel takes you somewhere and asks you to look through the eyes of another person, to live another life.

Barbara Kingsolver (born 1955), American novelist, essayist, and poet

The secret of joy is the mastery of pain.

Angela Anaïs Juana Antolina Rosa Edelmira Nin y Culmell (Anais Nin) (1903–1977), French–Cuban–American diarist, essayist, novelist and writer of short stories and erotica

Capsule

STING inhibits the reactivation of dormant metastasis in lung adenocarcinoma

Metastasis frequently develops from disseminated cancer cells that remain dormant after the apparently successful treatment of a primary tumor. These cells fluctuate between an immune-evasive quiescent state and a proliferative state liable to immune-mediated elimination. **Hu** et al. used models of indolent lung adenocarcinoma metastasis to identify cancer cell-intrinsic determinants of immune reactivity during exit from dormancy. Genetic screens of tumor-intrinsic immune regulators identified the stimulator of interferon genes (*STING*) pathway as a suppressor of metastatic outbreak. *STING* activity increases in metastatic progenitors that re-enter the cell cycle and is dampened by hypermethylation of the *STING* promoter and enhancer in breakthrough metastases or by chromatin repression in cells re-entering dormancy in response to TGFβ. *STING* expression in cancer cells derived from spontaneous metastases suppresses their outgrowth. Systemic treatment of mice with *STING* agonists eliminates dormant metastasis and prevents spontaneous outbreaks in a T cell- and natural killer cell-dependent manner. These effects require cancer cell *STING* function. Thus, *STING* provides a checkpoint against the progression of dormant metastasis and a therapeutically actionable strategy for the prevention of disease relapse.

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