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Tay Sachs in South Italy

Tay Sachs disease (TSD) is an autosomal recessive neurological disorder characterized by significant deficiency of lysosomal enzyme β-Hexosaminidase A and subsequent intralysosomal accumulation of GM2 ganglioside. The classical TSD occurs in early infancy with psychomotor retardation, blindness, seizures, macrocephaly and death within a few years. The "red cherry" spot is a typical fundoscopic finding due to intracellular accumulation of GM2 ganglioside, cholesterol and phospholipids. Late-onset TSD can be divided in subacute or "juvenile" and chronic or "adult" forms. Juvenile-onset cases usually occur in childhood with blindness, increasing spasticity and rigidity, seizures, dementia, progressing to a vegetative state in 5-15 years. Patients with adult-onset Tay Sachs develop signs of cerebellar involvement, ataxia, tremor, proximal muscle weakness, atrophy and sometime psychiatric symptoms. Late-onset TSD is characterized by variable age of onset, course and prognosis, even within the same family. More than 100 mutations in HEXA gene, encoding for the α-subunit of β-Hexosaminidase A, are responsible for deficiency or reduced activity of β-Hexosaminidase A. The residual enzyme activity correlates directly with disease severity. Tay Sachs disease has been extensively studied in the Ashkenazy Jewish population because of an elevated incidence of cases. In fact, the frequency of carriers, as defined by enzyme assay, among the Ashkenazy Jewish population in Israel and United States is of 1: 27 and 1:30 respectively. The frequency of TSD carriers is much lower among Caucasians (1:300).

We have described in a recent work a young woman of 30 years old with early onset depression at around age 9, inbalance with tendency to fall and cerebellar ataxia developed at 19 years old. She was no longer able to walk without assistance at age of 25. This patient originated from an isolated village of Calabria, South Italy. Genetic tests excluded recessive spinocerebellar ataxias. In vitro determination of the β-Hexosaminidase A activity showed a low value (< 10%) suggesting a diagnosis of TSD. Direct sequencing of HEXA gene revealed Gly269Ser mutation in compound heterozygosity with Leu127Arg. Gly269Ser is one of the most common mutations found in late-onset TSD, in both Jewish than non-Jewish populations. This genetic variation leads to a defect in the processing and association of α and β chains of β-Hexosaminidase A which retains, however, some residual activity. Conversely, Leu127Arg mutation is responsible for acute infantile onset of TSD in Italy. Several studies reported that patients with Gly269Ser showed milder and slowly progressive disease with more pronounced behavioral or psychiatric problems, and proximal weakness, as in the case reported by us.

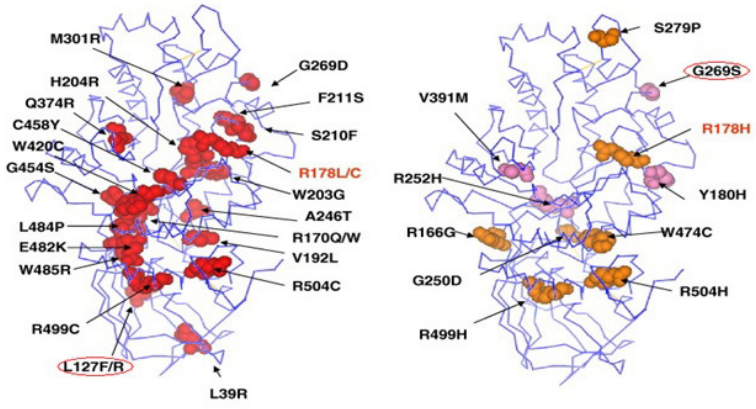

Fig. 1. Localization of missense mutations causing TSD in the three-dimensional structure of the human HexA subunit. Red circles point out the mutations found in our TSD case.

All cases with late-onset TSD reported in literature of Ashkenazi Jewish origin were compound heterozygotes for Gly269Ser and one of the infantile TSD mutations. Non-Jewish patients were more often homozygous for this mutation.

The identification of two different mutations in HEXA gene in the young woman reported by us originating from an isolated village of southern Italy, and the finding of consanguinity in the family (proband's parents were second-degree cousins), suggested the presence in this country of a founder effect of Ashkenazi Jews origin. In support of this hypothesis, historical sources indicated the presence of Jews in Calabria since eleventh century.

Fig. 2. Distribution of the Jewish community in the fifteenth century in Hither Calabria (province of Cosenza, Calabria, Italy).

In conclusion, our study emphasized the importance to identify the carrier state in the population from Calabria for an accurate genetic counseling. Furthermore, we suggested to consider the Tay Sachs disease in the differential diagnosis of spinocerebellar ataxia or atypical motor neuron disorders.

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