CANOMAD : clinical, biological, electrophysiological and treatment analyses in 44 patients. A French retrospective study of the FILO group.

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CANOMAD (chronic ataxic neuropathy, ophtalmoplegia, IgM paraprotein, cold agglutinins and disialosyl antibodies) is a rare syndrome characterized by chronic neuropathy with sensory ataxia, motor weakness affecting oculomotor and bulbar muscles, in the presence of an IgM paraprotein reacting against disialosyl antibodies. Other chronic ataxic neuropathies with disialosyl antibodies (CANDA), not meeting all criteria for CANOMAD, have also been described. Data regarding associated hematologic malignancies and effective therapeutic approaches in CANOMAD and CANDA are scarce in the literature.

We performed a French multicenter retrospective study that included 44 patients with a diagnosis of CANOMAD/CANDA syndrome from 2002 to 2018. Inclusion criteria consisted in the presence of serum IgM antibodies reacting against at least two distinct disialosyl epitopes in the context of evocating neurological signs.

Median age at diagnosis was 60,5 years (range, 39-81) and 33 patients (75%) were male. The median delay between occurrence of neurological signs and diagnosis was 60 months (range, 1-324). At diagnosis, 22 (50%) and 19 patients (43%) had respectively low (score 1 and 2) or more severe (score 3 to 5) disability Rankin score. Considering initial presentation and evolution, main clinical features were sensitive symptoms (ataxia, paraesthesiae, hypoesthesiae) (n=42, 96%), motor weakness, mostly affecting lower limb (n=18, 42%), ophtalmoplegia (n=16, 38%) and bulbar symptoms (n=5, 11%). Electrophysiological studies showed a demyelinating or axonal pattern in respectively 28 (64 %) and 16 patients (36%). An overt hematological malignancy was diagnosed in 14 patients (32%): Waldenström macroglobulinemia (WM) (n=10, 23%), chronic lymphocytic leukemia (n=1, 3%), mantle cell lymphoma (n=1, 3%), diffuse large B cell lymphoma (n=1, 3%), and unclassified B-cell lymphoproliferative disorder (n=1, 3%). Among the 30 other patients, 28 had an IgM

monoclonal gammapathy of undetermined significance. Among 42 patients with a detectable monoclonal IgM, median serum IgM spike was 2,21 g/L (range 0,1-40). The most frequent antibody association was GD1b+ GQ1b+ GT1b+ GD3+ (22 patients, 50%), and the serum of 34 patients (77%) contained IgM antibodies reacting against at least three or more of the four gangliosides. Cold agglutinins were identified in 13 (29%) patients. The median overall survival of the whole cohort was 14,9 years. The mean number of therapeutic lines was 2,6 (range, 0-9), for a total of 115 lines of treatment regarding the whole cohort. Among the 39 patients that received treatment, first lines consisted in intravenous immunoglobulins (IVIg) (n=21, 48%), corticosteroids (n=11, 28%), chlorambucil (n=4, 10%), plasmapheresis (n=2, 5%), rituximab (n=1, 2,5%) and azathioprine (n=1, 2,5%). One patient had and association of corticosteroids and chlorambucil. IVIg and rituximab were used, as first or subsequent lines of treatment, in respectively 54 and 19/115 total cases. Complete or partial clinical responses were observed for IVIg in 22/54 (41%) and for rituximab in 9/23 (39%) cases. Immunosuppressive therapies (corticosteroids, cyclosporine, azathioprine and cyclophosphamide) were less effective (5/38, 13%).

In conclusion, CANOMAD/CANDA syndromes are rare, misdiagnosed and debilitating syndromes, which are associated with an overt hematological malignancy, mainly WM, in one third of the patients. IVIg and rituximab are the most effective therapies.