National Tay-Sachs &
Allied Diseases Association

Information for Psychiatric Providers on Treatment of Psychiatric Symptoms in Late-Onset GM2 Gangliosidosis

These general recommendations are the results of the ad hoc working group "psychiatric aspects of Late-onset GM2 Gangliosidoses" (LOGG) comprised of psychiatrists and neurologists who treat patients with these conditions and was organized by National Tay-Sachs & Allied Diseases Association (NTSAD). Core members of the working group included: Camilo Toro, MD (National Institutes of Health); Christopher Stephen, MB ChB, FRCP, SM (Massachusetts General Hospital); Sonja Scholz, MD, PhD (National Institutes of Health); Steven Kushner, MD, PhD (Columbia University Vagelos College of Physicians and Surgeons); Caitlin Adams, MD (Massachusetts General Hospital).

Late-Onset GM2 Gangliosidoses (LOGG), comprising Late-Onset Tay-Sachs (LOTS) Disease and Sandhoff Disease (LOSD), are complex genetic movement disorders caused by mutations in the HEXA (LOTS) and HEXB (LOSD) genes, which encode the **α** and **β** subunits, respectively, of hexosaminidase A (**αβ**) and hexosaminidase B (**β**2). Both disorders result in deficient hexosaminidase A activity and the accumulation of GM2 ganglioside, which is important for a variety of neurological functions. In comparison to infantile and juvenile GM2 gangliosidosis, late-onset cases present in late childhood (generally above age 10), survive well into adulthood, and typically present with a combination of weakness (with a predilection of involvement of the triceps and quadriceps muscles) and cerebellar ataxia, with some cases developing a cognitive disorder and neuropsychiatric symptoms (1).

It is estimated that roughly 30-50% of patients may develop psychiatric symptoms throughout the disease course (2), as both a primary disease manifestation as well as related to the patient coping with the symptoms of the disease (1,2). More specific and pathological psychiatric symptoms can mimic bipolar affective disorder (with or without manic symptoms), and psychosis, which can mimic schizophrenia (2). It has been suggested that these symptoms may represent the Cerebellar Cognitive Affective Syndrome (3).

Of these two disease subtypes, LOTS appears much more likely to present with prominent psychiatric symptoms, particularly in younger patients with LOTS, and also tend to present early in the disease course4, sometimes as an initial disease manifestation5. In comparison, whereas there are far fewer cases reported of LOSD, in those that are reported, psychiatric symptoms tend to similarly occur in younger patients with LOSD (4).

Although limited, LOTS patient survey data published by Shapiro et al. in 2006 suggests that certain psychiatric medications may be less efficacious in LOTS, and that some may even lead to worsening of neurological symptoms (loosely described as "increased weakness, incoordination, imbalance, tremor, dysarthria, dystonia, cognitive decline, or worsening psychiatric symptoms") (6). It may be that these data can be extrapolated to LOSD, given their similar disease mechanisms, but this assumption is not currently supported by any data.

Psychiatric medications reported by Shapiro et al. that were associated with worsening neurological or psychiatric symptoms (with percentages calculated as the fraction of those who reported worsening compared to all that reported taking the medication) can be used as a rough risk estimate for LOGG patients6. As a caveat, unless otherwise noted, the number of patients taking each individual medication ranged from age 4 to 13.

- Antipsychotics: Haloperidol (80% worsened), risperidone (83.3% worsened), and chlorpromazine (100% worsened)
- Mood stabilizers: Lithium (27.3% worsened), valproic acid (62.5% worsened), and carbamazepine was the least problematic (7.7% worsened)
- Antidepressants: These were generally well-tolerated, although those with a higher proportion of neurological worsening included bupropion (50% worsened) and sertraline (33% worsened). Only one patient reported worsening with paroxetine, mirtazapine, and amitriptyline. The only medication that was beneficial and had no associated neurological worsening was citalopram.
- Benzodiazepines/anxiolytics: Lorazepam, clonazepam and alprazolam most often provided benefit, with neurological worsening reported for lorazepam (17%), diazepam (50%), and in a single patient, alprazolam only at high doses.
- Stimulants: Only methylphenidate was reported in 4 patients, with neurological worsening in 50%.
- Electroconvulsive therapy: ECT resulted in psychiatric benefit in 2 of 3 patients reported, one of whom also had neurological worsening; the third patient had no psychiatric improvement but had neurologic worsening.

National Tay-Sachs & Allied Diseases Association (NTSAD), a trusted patient advocacy organization dedicated to leading the worldwide fight to treat and cure Tay-Sachs, Canavan, GM1, and Sandhoff diseases, is interested in improving awareness of this seldomly discussed aspect of LOGG, and particularly those with LOTS. The NTSAD Family Services team separately conducted a survey of 20 patients with LOGG and 10 caregivers/spouses. According to this survey, psychiatric medications that were associated with worsening symptoms included haloperidol, carbamazepine, lithium, and mirtazapine. However, the efficacy of these medications was not assessed.

References

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