Purpose: We present 2 cases of LHON with atypical onset and clinical course. Both probands carried a rare mtDNA pathogenic mutation affecting complex I, and experienced significant improvement of visual function during treatment with idebenone. Methods and results: The patients have been followed with serial assessments of visual acuity, visual fields and OCT. In one case a novel mtDNA mutation (m.1477A in MT-ND6 gene) was found by sequencing analysis, whereas in the other the mtDNA mutation (m.13051G in MT-ND5 gene) was previously described only in three cases from a Dutch pedigree. Environmental factors possibly played an important role in triggering the clinical onset of the disease. In both cases the disease onset followed a major episode of depression with heavy abuse of alcohol and smoking. Both patients showed a dramatic and steady improvement of visual function during the first few months of treatment with idebenone (600 mg die). This improvement was stable after 2 years. Conclusions: Certain LHON cases may be associated with rare mtDNA mutations, different from the three commonly found. These cases might be misdiagnosed as tobacco-alcohol or toxic optic neuropathy. Consistent recovery of visual function may be observed with idebenone in these cases. Financial Disclosure: None