Molecular Genetics and Metabolism Reports 10 (2017) 20–22

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Correspondence

Low dose clozapine controls adult-onset psychosis associated with the neurogenic ataxia-retinitis pigmentosa (NARP) mutation

Keywords:
NARP syndrome
m.8993T>C mutation
Clozapine
Myoclonus
Myoclonic seizures
Psychosis
Mitochondrial disease

Little is known regarding the management of psychotic disorders in NARP syndrome. We report the case of a 30 year-old Caucasian male, born from healthy unrelated parents. During his first year, he presented cerebellar ataxia with pyramidal syndrome. Sequencing his leukocyte and urinary mtDNA detected a heteroplasmic mutation (95%) in the MTATP6 gene (m.8993T>C) [1]. At 28 years, he presented a psychotic episode with psychomotor agitation and delusional persecutory beliefs without cognitive decline. Brain MRI showed a cerebellar atrophy and bilateral striatal hyper-intensities (Fig. 1A). Antipsychotics lead to dystonia, akathisia and extrapyramidal syndrome with falls. The patient remained aggressive with faecal and urinary incontinence. Thus, a switch to clozapine was suggested [2]. Clozapine was administrated at low dose (12.5 mg/day, reaching 37.5 mg/day in four weeks). The patient experienced a complete remission of paranoid delusions and violent behavior. Owing to occurrence of lower limb negative myoclonus, falls and fatigue, clozapine intake was lowered to 25 mg/day. As a result, delusions resumed a few days later. Eventually, an alternative clozapine administration (37.5 mg/25 mg every other day) was started, which alleviated psychiatric symptoms and improved extrapyramidal side effects (Fig. 1B). The effectiveness of clozapine on psychotic disorders is supported by the control of paranoid delusions when administered at efficient doses and its relapse when drug intake was reduced. It is worth noting, however, that the doses of clozapine used here are far lower than the ones required for control of resistant schizophrenia (300–900 mg/day) [3]. Clozapine has strong affinity for several dopaminergic receptors and is also a serotonin antagonist with strong binding to 5-HT2A/2C receptors [4]. Efficacy and safety of low doses of clozapine have been previously shown in Parkinson's disease [5,6,7]. Further studies will hopefully confirm the interest of low dose of clozapine for psychotic symptoms in NARP syndrome, and maybe other mitochondrial disorders.

Competing interests

None.

Acknowledgments

"Conseil Scientifique et de la Recherche", Vinatier Hospital, Bron, France.

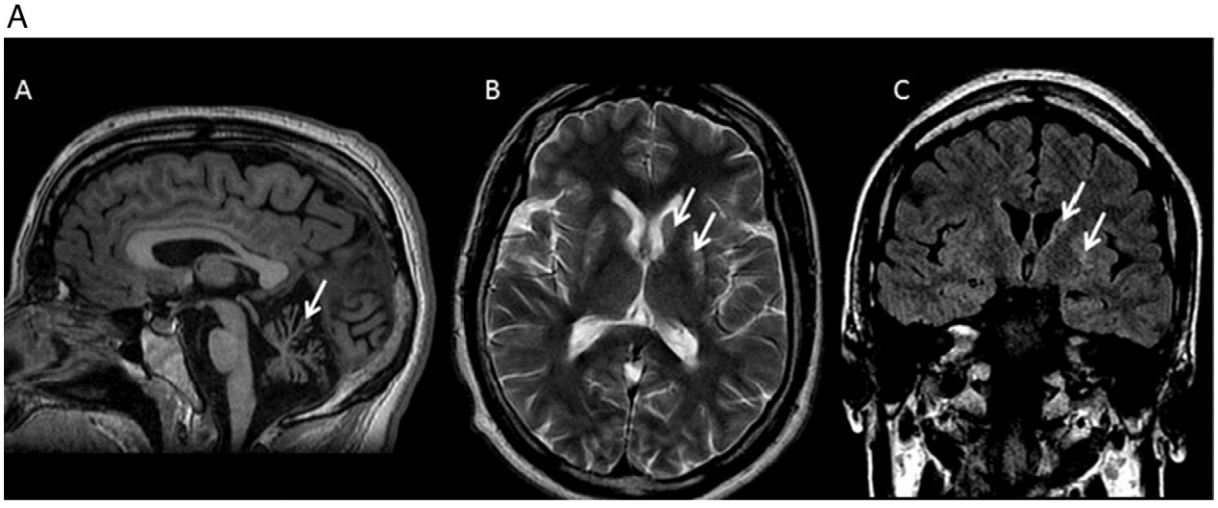

Fig. 1. A. Brain MRI of the 30 years-old affected patient (A, B, C). Sagittal T1 weighted image (A) shows an important cerebellar atrophy (arrow). The axial T2 (B) and coronal Flair (C) weighted images show bilateral abnormal hyperintensities in putamen and caudate nuclei (arrows in abnormal striatum). B: Pre/clozapine treatment assessment. Major symptoms: ++; Moderate symptoms: +; Absence of symptoms: 0; *: based on the patient's interview and reports of the family members; **: based on reports of family members; CGI-I: Clinical Global Impressions-Improvement; BPRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Syndrome Scale.

http://dx.doi.org/10.1016/j.ymgmr.2016.12.003

B

	Pre-treatment	Clozapine treatment (37,5 mg/25 mg/day in alternance)
CGI – I score*		2
BPRS score*	63	31 (-51%)
PANSS score* *positive scale (min=7 ; max=49)*	31	14 (-55%)
negative scale (min=7 ; max=49)	26	24 (-8%)
general psychopathology scale (min=16 ; max=112)	66	34 (-52%)
Blood test for clozapine monitoring	Normal values	Normal values
Telephone adverse symptoms checklist		Week 1: asthenia and myoclonus Week 2:asthenia and myoclonus Week 3: myoclonus Week 4: myoclonus
Cerebellar ataxia	+	+
Pyramidal symptoms	+	+
Dysarthria	+	+
Myoclonic seizures	+	+
Myoclonus	-	+
Vasovagal episodes	+	_
Extrapyramidal syndrome	++	+
Tremor	+	-
Dystonia	++	+
Akathisia (feeling of internal motor restlessness with tension and anxiety)	+	-
Headaches	+	-
Faecal incontinence	++	-
Urinary incontinence	+	-
Asthenia	++	+

*Major symptoms: ++ ; Moderate symptoms: + ; Absence of symptoms: 0 ; *: based on the patient's interview and reports of the family members ; **: based on reports of family members ; CGI-I: Clinical Global Impressions-Improvement ; BPRS: Brief Psychiatric Rating Scale ; PANSS: Positive and Negative Syndrome Scale*

Fig. 1 (*continued*).

References

[1] C.L. Alston, L. He, A.A. Morris, I. Hughes, C. de Goede, D.M. Turnbull, R. McFarland, R.W. Taylor, Maternally inherited mitochondrial DNA disease in consanguineous families, Eur J Hum Genet 19 (2011) 1226–1229.

[2] A.M. Williams, S.H. Park, Seizure associated with clozapine: incidence, etiology and management, CNS Drugs 29 (2015) 101–111.

[3] D. Siskind, L. McCartney, R. Goldschlager, S. Kisely, Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis, Br J Psychiatry 209 (2016) 385–392.

[4] M.C. Mauri, S. Paletta, M. Maffini, A. Colasanti, F. Dragogna, C. Di Pace, A.C. Attamura, Clinical pharmacology of antipsychotics: an update, EXCLI J 13 (2014) 1163–1191.

[5] J.Q. Kwong, M.F. Beal, G. Manfredi, The role of mitochondria in inherited neurodegenerative diseases, J Neurochem 97 (2006) 1659.

[6] O.O. Ojo, H.H. Fernandez, Current understanding of psychosis in Parkinson's disease, Curr Psychiatry Rep 18 (2016) 97, http://dx.doi.org/10.1007/s11920-016-0730-1.

[7] N. Divac, R. Stojanović, K. Savić Vujović, B. Medić, A. Damjanović, M. Prostran, The efficacy and safety of antipsychotic medications in the treatment of psychosis in patients with Parkinson's disease, Behav Neurol 4938154 (2016)http://dx.doi.org/10.1155/2016/4938154.

Caroline Demily*
Alice Poisson
GénoPsy, Centre Hospitalier le Vinatier et Centre de Neuroscience Cognitive, UMR 5229 (CNRS et Université Claude Bernard Lyon 1), Bron, France
*Corresponding author.
E-mail address: caroline.demily@ch-le-vinatier.fr (C. Demily)

Charlyne Duwime
Association l'Elan Retrouvé, Paris, France

Nathalie Boddaert
INSERM U1163, Université Paris-Descartes, Service de radiologie pédiatrique, Institut Imagine, Hôpital Necker-Enfants Malades, Paris, France

Arnold Munnich
INSERM UMR 1163, Université Paris Descartes-Sorbonne, Service de génétique clinique, Institut Imagine, Hôpital Necker-Enfants Malades, Paris, France

7 December 2016