*Psychiatria Danubina, 2021; Vol. 33, Suppl. 4 (part IV), pp 1254-1260* *Conference paper*

*Review*

# TRANSDISCIPLINARY APPROACH IN TYPE I NEUROFIBROMATOSIS - REVIEW OF PSYCHIATRIC DISORDERS

**Marija Bogadi[1], Ivana Bakija[2], Snježana Kaštelan[3,4] & Boris Kasun[5]**

*[1]Psychiatry Hospital for Children and Adolescents, Zagreb, Croatia*
*[2]Psychiatry Hospital „Sveti Ivan", Department of Integrative Psychiatry, Zagreb, Croatia*
*[3]School of Medicine, University of Zagreb, Zagreb, Croatia*
*[4]Department for Ophthalmology, Clinical Hospital Dubrava, Zagreb, Croatia*
*[5]Special Hospital for Medical Rehabilitation Stubičke Toplice, Stubičke Toplice, Croatia*

## *SUMMARY*

***Background:*** *Neurofibromatosis type 1 (NF1) is an autosomal dominant a multisystem genetic disorder that primarily involves the skin and the nervous system. The incidence of the disease is 1:3000-4000 live-born children, equally in both sexes. The diagnosis of NF1 is determined individually with any two of the following clinical features: café-au-lait spots, intertriginous freckling, Lisch nodules, neurofibromas, optic glioma, distinctive bone lesions and first-degree family relative with NF1. NF1 is a disease most commonly diagnosed and treated by neuropediatricians.*

***Results:*** *Cognitive and behavioral disorders affect between 50-80% of all children with NF1. Children with NF1 show impairments in attention, visual perception, language, executive function, academic skills, and behavior. This requires a multidisciplinary approach to the treatment s as seen in the case we present. Furthermore, NF1 is often associated with psychiatric disorders, which are more frequent in this disease than in general population, according to some studies even up to 33% patients. Psychiatric disorders are more frequent in NF1 than in the general population, particularly in children. They include dysthymia, depressive mood, anxiety, and personality disorders. Bipolar mood disorders or schizophrenia are rather rare. The majority of studies have focused on physical health and neurocognitive function in NF1, whereas psychiatric disorders associated with this disease remain unclear and poorly documented.*

***Conclusions:*** *We present a case of an eight-year-old boy with behavioural and learning disabilities referred for psychological and psychiatric evaluation as well as an overview of NF-related psychiatric illnesses described in the literature.*

***Key words:*** *neurofibromatosis - mental disorders - cognitive difficulties – ADHD - autism*

* * * * *

## INTRODUCTION

"Neurofibromatosis" (NF) is a genetic disorder that is commonly associated with the appearance of nerve tumours and include NF1 or von Recklinghausen disease, NF2 and schwannomatosis. All of these disorders are predominantly inherited with a high rate of new mutations with variable expression. NF1 is the most common and includes changes of multiple body systems with neurofibroma being the most frequent type of tumour. Schwanomas of multiple cranial and spinal nerves, especially the vestibular nerve, as well as meningiomas and ependymomas are present in NF2. The genes underlying each of the disorders include NF1 for type 1 neurofibromatosis located on chromosome 17q11.2, NF2 for type 2 neurofibromatosis, and INI1 / SMARCB1 for schwannomatosis (Evans et al. 2010). Diagnostic criteria for NF1 include alterations in skin pigmentation (café au lait spots, skinfold freckling), Lisch nodules and nervous system tumours namely neurofibromas and optic pathway gliomas. Clinical manifestations are bone dysplasia, learning disabilities and increased risk for malignancy (Huson 1989). The incidence of NF1 birth is 1 in 2700. It is considered a predisposition to cancer syndrome, with the most common complication in childhood being inadequate academic achievement and cognition difficulties, which affect attention, executive, language, and visual-spatial function (Hyman et al. 2005, Hyman 2006, Lehtonen et al. 2013, Payne 2013). In addition, patients with NF1 often experience psychiatric difficulties, autistic and hyperkinetic disorders which complicate their daily functioning (Bogadi et al. 2018). In this paper out intention was to highlight the existence and importance of psychiatric and cognitive disorders in NF1 stressing the need for a multidisciplinary approach. A clear overview of all mental disorders and difficulties faced by people affected by this disease will lead to more successful forms of treatment and improve the quality of life (QOL) of patients with NF1 in general.

## DISCUSSION

### Psychiatric diseases and neurofibromatosis type 1

Neurofibromatosis type 1 is often associated with psychiatric disorders, which are more frequent in NF1 patients than in the general population (33% of patients). Belzeaux & Lançon (2006) reported that dysthymia is the most common psychiatric diagnosis (21%) in patients with NF1. In the same study they found a high prevalence of depressed mood (7%), anxiety (1-6%) and personality disorder (3%). The risk of suicide

was four times higher than in the general population, and bipolar mood disorders or schizophrenia appeared to be rare. They considered that impaired QOL associated with NF1 may play an important role in the development of psychiatric disorders (Belzeaux & Lançon 2006). The same result was obtained by Zöller & Rembeck (1999) in the study regarding the impact of NF1 on psychiatric symptoms and diagnosis, personality variables, and self-evaluation over 12 years in patients in Gothenburg, Sweden. Significant psychopathology was found in patients with NF1 with one third of the patients being affected by psychiatric illness, and 21% by dysthymia. Another study conducted over a 12 year period examined neuropsychological deficits in adults with NF1 with and without an affective mental disorder such as dysthymia (Zöller et al. 1997). The results of these trials indicated NF1-related deficits in inductive reasoning, visual-constructive skills, visual and tactual memory, logical abstraction, coordination and mental flexibility, although basic motor speed and vocabulary were not influenced by NF1. An affective disorder exacerbated the neuropsychological deficits associated with NF1 only with regard to tests assessing motor functions. They concluded that NF1 results in a relatively global cognitive impairment among adults with additional depressive symptoms slowing down basic motor processes. Cohen et al. (2015) measured the prevalence of depressive symptoms among a large group of adults with NF1 in order to quantify the impact of depressive symptoms on QOL using the Center for Epidemiologic Studies Depression (CESD) scale. Results showed that 55% of all participants (61% of females and 43% of males) had scores above 16, indicating a high likelihood of clinical depression. Depressive symptoms measured by the Quality of Life Index accounted for 32% of the variance in QOL using a multivariate regression model controlling for demographics and potential confounders. These findings provide strong evidence that patients with NF1 have higher risk for psychiatric disorders implicating that they should undergo routine testing for depression due to the strong correlation with QOL.

Psychiatric disorders are more frequent in NF1 than in the general population, particularly in children. The current literature does not provide full explanations of anxiety symptoms associated with NF1. Some authors have tried to explain the link between NF1 and psychiatric disorders, and several etiopathogenic hypotheses have been proposed. Fekih-Romdhane et al. (2015) presented a case report of a 13 year old child diagnosed with NF1 and anxiety disorder. Anxiety symptoms appeared before the age of 4 increasing gradually over time. This strengthens the hypothesis of genetic determinism in NF1 patients. This raises the question of whether it is a random association of psychiatric disorders and NF1 or whether psychiatric manifestations are induced by multisystemic disease. More detailed investigations are necessary to clarify the etiopathogenic and psychopathological mechanisms that would cause psychiatric comorbidity associated with NF1.

It is known that NF1 is a neurodevelopmental disorder placing both children and adults with this diagnosis at a higher risk of developing sleep disorders (Anastasaki et al. 2019). Maraña Pérez et al. (2014) in their comparative retrospective study included 95 paediatric patients with NF1 who completed the Bruni Sleep Disturbance Scale in Children. Patients with NF1 and IQ<85 showed higher prevalence rates of daytime sleepiness and of sleep hyperhidrosis and found a statistically significant difference in the subdomain of nocturnal hyperhidrosis. A prospective study of sleep quality in 114 consecutive patients with NF1 was performed by Leschziner et al. (2013). The Epworth sleepiness scale (ESS) and the Pittsburgh sleep quality index (PSQI) were administered. Data regarding drugs with potential impact on sleep, complications directly affecting sleep and employment status was also collected. The mean ESS was 6.8, and 21% had an abnormally high ESS of 10 or more. The mean global PSQI score was 8.4 (norm mean 2.67), with abnormally high scores in all sleep domains. Thirty-nine patients had a bed partner and 54% reported features suggestive of periodic limb movements of sleep, 43% had features suggestive of obstructive sleep apnoea and 10.8% experienced confusion on waking. The authors concluded that sleep disturbance and poor quality of sleep are significantly more frequent in the adult NF1 patient population.

Some researchers have studied the association between NF1 and mental retardation. Samuelsson & Riccardi (1989) reported 23 cases of mental illness (33%) of the 69 participants with NF-1. In their report, moderately severe or severe mental illness, corresponding to grade 2 and 3 according to the Comprehensive Psychopathological Rating Scale (CPRS), was found in 15 of the 69 patients (22%). The 23 mentally ill patients did not show any uniform clinical psychiatric syndrome. The most commonly occurring psychiatric diagnoses were depressive syndrome, anxiety state with vegetative dysfunction and organic brain syndrome. There was a significant positive relation between depressive syndrome and organic brain syndrome according to the CPRS rating. Half of the patients complained of mental symptoms in the form of hostile feelings and autonomic disturbances which were the most frequent psychiatric symptoms.

Some researchers have attempted to explain whether psychiatric and developmental disorders are over-represented in patients with NF1 particularly when NF1 patients are compared to those with other chronic neurological disorders (DeFries et al. 1976). Extensive, interesting and valuable research assessing general somatic, psychiatric, social and genetic aspects

of NF l in a carefully defined population of residents of Gothenburg in Sweden was conducted (Samuelsson & Samuelsson 1989a, Samuelsson & Riccardi 1989b, Samuelsson & Riccardi 1989c). In that research 45% of patients with NF1 showed slight mental retardation with two showing a greater level of retardation. This mild mental retardation was usually recognized during the early school years and it did not appear to be progressive. Patients affected with this problem were placed in remedial or special classes in school. There is reason to suspect that NF 1 itself leads to some impairment of intellectual development in all patients. The intellectual achievements of participants whose intelligence was judged to be within the normal range appeared to be less than average. None of the patients with normal intelligence had passed any academic examination. Many of them showed achievements less than expected based on the achievements of their healthy relatives. In certain families, the NF appeared to be associated with mild mental retardation more than in other families. Mental retardation of a more severe degree, corresponding to special school level or lower, is not typical of NF1 (Samuelsson & Riccardi 1989b).

Recently, greater attention has been given to the association of posttraumatic stress disorder (PTSD) and various diseases particularly those with chronic duration. Huguen et al. (2018) investigated the occurrence of PTSD in patients with NF and found a high level of PTSD following sporadic NF1 disclosure, particularly in the parents of children with NF1. It is still not clear whether this is coincidental or wether a real causal connection between psychotic disorders and NF1 exists (Mirza & Majeed 2018).

## Autistic disorder and neurofibromatosis type 1

Many articles reporting an association between NF 1 and autistic disorders exist. Autism is characterized by changes in behaviour in all areas of the central nervous system (CNS): motoric, perceptual, intellectual, emotional and social. According to the Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) classification and International Classification of Diseases-10 Edition the essential feature of autistic disorder is the abnormal or impaired development of social interactions and communication, a markedly reduced repertoire of activity and interest as well as manifestations of disorder differing according to developmental stage and chronological age (Bujas Petković 2010). Eijk et al. (2018) found that the prevalence rate of autism spectrum disorder (ASD) in children with NF1 was 10.9%, which is higher than in the general population estimated at 3-6 per 10,000. They concluded that the combined observational and screening based classifications demonstrated the highest positive predictive value for DSM-IV diagnosis, highlighting the importance of using both approaches in children with NF1.

Molosh & Shekhar (2018) also indicated a higher incidence of ASD in NF1 patients. Recently, results of meta-analysis of social function and ASD in children and adults with NF1 have been published with the results proving that children and adults with NF1 show a significantly higher prevalence and severity of social dysfunction and ASD symptomatology. The results further support the presence of age, sex and comorbid ADHD as moderating factors for social outcomes in NF1 (Chisholm et al. 2018). Walsh et al. (2013) included sixty-six participants (42 males, 24 females) in their study with the mean age at assessment being 10 years and 11 months. Difficulties in neurocognition and social interaction are the most prominent causes of morbidity and long-term disability in children with NF1 with patients with ASD showing significantly impaired social interaction. Further they found that 40% of the NF1 sample had raised symptom levels reaching clinical significance on the Social Responsiveness Scale ($T \geq 60$), and 14% reached levels consistent with those seen in children with ASDs ($T \geq 75$). These raised levels were not explained by NF1 disease severity or externalizing/internalizing behavioural disorders. Obtained results were consistent with previous reports.

## Attention deficit hyperactivity disorder and neurofibromatosis type 1

Hyperactivity or hyperkinesis disorder (attention deficit hyperactivity disorder - ADHD) is defined as a trias involving hyperkinesia, attention deficit and impulsivity (Juretić & Škevin 2004). The incidence of ADHD in patients with NF1 ranges between 33% and 49.5% and is equally common in both sexes (Basu et al. 1992). According to Payne (2012), approximately 40% of children with NF1 meet diagnostic criteria for ADHD. The mechanisms responsible for ADHD symptoms appear to differ in patients with NF1 and those without NF1, which include complex impairments of cognitive processes, visual-spatial function and executive function (Hyman et al. 2005, Sanchez-Marco et al. 2019). Some researchers have suggested that impaired reactivity to visual signals may play a substantial role (Hyman et al. 2006). Sanchez-Marco et al. (2019) conducted research with 56 NF1 patients of which 23 of patients (41%) being diagnosed with ADHD and the mean age at diagnosis being 7.53±2.46 years. School-age children with ADHD represented 48.8% of the cases. All but one of the children received treatment and the mean duration of treatment was 3.85±3.04 years. Positive effects were reported by 11 patients with a moderate response in eight patients. The research results confirm the high prevalence of ADHD in patients with NF1. Several studies suggest that cognitive, motor, learning, and social problems often identified in patients with NF1 are a direct consequence of NF1 pathology (Lidzba et al. 2012). Koth et al. (2000) compared the ADHD status of children with NF1 to that of their healthy siblings and

biological parents and found a significant connection between NF1 and ADHD, suggesting that ADHD occurs as a component of the underlying disease.

Payne et al. (2012) conducted research with 49 children aged 7 to 15 years with only NF1, 35 with NF1 and ADHD and a control group of 30 healthy children. They investigation addressed whether spatial working memory and response inhibition were impaired in children with NF1 without a diagnosis of ADHD and whether executive deficits worsened in children with a comorbid diagnosis. The results of the research found no differences between the two NF1 groups in spatial working memory ($p=0.91$) or response inhibition ($p=0.78$). Given that executive dysfunction occurs with the same severity in children with NF1, regardless of the presence of a comorbid diagnosis of ADHD, can be assumed that executive impairments are not unique contributors to ADHD symptomatology in NF1.

Pride et al. (2012) obtained opposing results when comparing cognitive functioning, academic ability and the predictors of academic underachievement. They compared these functions in children with NF1, children with NF1 and comorbid ADHD and unaffected controls. Their results indicated that the presence of ADHD affects some aspects of cognitive functioning and learning in NF1 patients. Inattention and executive dysfunction are general characteristics of the NF1 cognitive phenotype and significantly undermine academic achievement of children with NF1.

Learning and developmental disorders as the most common neurologic complications of NF1 can be responsible for significant lifetime morbidity. Cohen & Shuper (2010) conducted a review on cognitive and developmental manifestation of children with NF1 stressing the importance of early diagnosis and treatment.

Neurofibromatosis type 1 is a common neurologic condition associated with a wide variety of developmental deficits that have an important impact on children and adolescents. Based on a review of the literature concerning the social life, mental health and QOL of children and adolescents with NF1 as well as the psychosocial interventions addressed to this population, Domon-Archambault et al. (2018) concluded that there is a need to develop and assess psychosocial interventions for patients with NF1. Comparing unaffected children and adolescents of the general population with paediatric NF1 patients they found that children with NF1 have an increased risk for social difficulties, mental health disorders, behavioural and emotional problems, as well as diminished QOL. Garcia-Penas (2017) researched neurocognitive deficits and academic learning difficulties as the most common neurologic complication of NF1 in childhood. Children with NF1 showed impairments in attention, visual perception, language, executive function, academic skills, and behaviour. A study in animal models suggest that learning disabilities associated with NF1 are caused by excessive Ras activity that leads to increased gamma-aminobutyric acid (GABA) inhibition and to decreased long-term potentiation (Garcia-Penas 2017). Garcia-Penas (2017) found that cognitive and behavioural disorders affect between 50-80% of all children with NF1. There are three subtypes of cognitive profiles in children with NF1 and learning disorders, including global learning disorder, specific learning disorder and isolated ADHD. The most common cognitive deficits are connected with visual-spatial impairment, however working memory and executive function deficits associated with prefrontal cortex dysfunction are also important. Hyman et al. (2005) found extremely high frequency of cognitive deficits in children with NF1. Extensive cognitive assessments were performed in 81 children with NF1 aged 8 to 16 years and 49 unaffected sibling controls. Eighty-one percent of the children with NF1 had moderate to severe impairment in one or more areas of cognitive functioning. Although 51% of children with NF1 performed poorly on tasks of reading, spelling and mathematics, specific learning disabilities (as defined by IQ-achievement discrepancies) were present in only 20% of the children. Sustained attention difficulties were present in 63% of children with NF1, with 38% of children with NF1 fulfilling the diagnostic criteria for ADHD. The NF1 neuropsychological profile is characterized by deficits in perceptual skills (visual-spatial and visual-perceptual), executive functioning (planning and abstract concept formation), and attention (sustained and switching). Both verbal and visual memory were unaffected in NF1 children and their memory skills were generally stronger than their level of general intellectual function. Although both expressive and receptive language skills were significantly impaired in NF1 children, they appeared to be relatively better preserved than visual-spatial abilities once IQ is taken into account (Hyman et al. 2005). Martin at al. (2012) in their study presented psychological assessments of 53 children (mean age 12.4 years). Parents and teachers completed the behaviour assessment system for children-second edition (BASC-2). The severity of the disease was quantified as well as the burden of the tumor, and parents filled out a list of life events to point out environmental stressors. The results showed that cognitive skills, the disease itself and environmental variables affect socio-emotional outcomes in children with NF1. These children can benefit from interventions focused on social skills, cognitive functioning, and the ability to adapt as means of coping with NF1-related difficulties.

## Psychosocial skills and neurofibromatosis type 1

Cipolletta et al. (2018) conducted a study which showed that the psychological functioning, behaviour, self-image and QOL of children and adolescents with

NF1 are compromised. Individuals with NF1 reported anxiety problems, poorer QOL and greater distortions in terms of self-image. The parents of NF1 participants reported having more concerns regarding the QOL, sociality, school performance and attention span of their children. Researchers concluded that health services should take into account the psychosocial difficulties associated with NF1 and design rehabilitation programs aimed at increasing NF1 children's interpersonal skills, improving their social life and QOL. Focus should also be aimed at promoting more adaptive behaviours and health care interventions which involve the parents of children with NF1. (Domon-Archambault et al. (2018) obtained similar result when comparing unaffected children and adolescents of the general population with paediatric patients with NF1. They found that patients with NF1 experience an increased risk of having social difficulties, mental health disorders, behavioural and emotional problems as well as diminished QOL. In the study regarding the association of neuropsychological status and social skills deficits in patients with Noonan syndrome and NF1 showed that five percent of the children with NF1 were rated as having severe social skills impairment (Pierpont et al. 2018).

Visual attention to faces in social situations in children with NF1 and healthy peers was also examined. Children with NF1 spend less time paying attention to faces than typically developing children when presented in social situations. These findings suggest that abnormal face processing is a key aspect of the social-cognitive phenotype of NF1 and appears to be related to autism spectrum disorder traits. Children with NF1 demonstrated atypical gaze behaviour when paying attention to faces which was characterized by normal initial fixation on faces but shorter retention time. Decreased attention to faces was associated with elevated autism traits in the sample with NF1 (Lewis et al. 2018). More recently, the possibilities of innovative applications of social media dedicated to those who care for children with chronic conditions can provide peer-to-peer support, shared experience, and reliable medical information. The availability of this innovative approach can break isolation these children, enable connection with other families and provide accurate information, advice and support from others facing similar challenges. The opportunity to communicate with others regarding the challenges they are faced with is very valuable and the shared experiences provide them with a sense of normalcy (Akre et al. 2018).

We presented a case of an eight-year-old boy with type I NF who came for multidisciplinary treatment. The diagnosis NF1 was confirmed during his ophthalmologic treatment of strabismus at the age of two. His father as well as both of his younger brothers were also diagnosed with the same illness. When the boy was attending second grade of primary school he started showing difficulties in mastering the academic program. The ophthalmologic examination also confirmed, along with strabismus, visual impairment of both eyes with visual impairment being slightly more pronounced in the right eye. The best-corrected visual acuity of the right eye was 0.5 and left eye 0.8. The child patient was included in multidisciplinary treatment due to psychomotor disorder, attention deficit, impulsiveness, hyperactivity, peer relationship issues, emotional difficulties, problems in understanding and memorizing school material as well as reading and writing.

After evaluation, the appropriate form of education was determined and the boy was including speech therapy, special education and psychiatric treatment with the aim of reducing psychomotor disorder and assistance in learning and thereby reducing frustration and improving self-esteem. Also, parents were suggested counselling and support.

## CONCLUSION

The presence of a high incidence of autistic disorder, hyperkinetic disorder and cognitive problems in individuals with NF is well documented. Previous studies indicate the importance of involving a psychiatrist using the multidisciplinary approach in diagnosis and treatment of patients with NF. Early diagnosis, better communication and the possibility of pharmacological therapy will aid the integration of patients into society. Current knowledge points to the need for further research in order to clarify the role of psychiatric disorders in patients with NF1.

***Acknowledgements:*** None.

***Conflict of interest:*** None to declare.

***Contribution of individual authors:***

Marija Bogadi: idea, concept and design of article, literature searches, writing manuscript, approval of final version.

Snježana Kaštelan: concept and design of article, literature searches, writing some parts of manuscript, approval of final version.

Ivana Bakija, Marta Gotovac, Boris Kasun: comments on the concept of article, literature searches, approval of the final version.

## References

1. *Akre C, Polvinen J, Ullrich NJ, Rich M. Children's at Home: Pilot Study Assessing Dedicated Social Media for Parents of Adolescents with Neurofibromatosis Type 1. J Genet Couns 2018; 27:505-517*
2. *Anastasaki C, Nicholas Rensing N, Johnson KJ, Wong M, Gutmann DH, Neurofibromatosis type 1 (Nf1)-mutant mice exhibit increased sleep fragmentation. J Sleep Res 2019; 28:e12816*

3. *Basu TN, Gutmann DH, Fletcher JA, et al. Aberrant regulation of ras proteins in malignant tumour cells from type 1 neurofibromatosis patients. Nature 1992; 356:713-5*
4. *Belzeaux R & Lançon C: Neurofibromatosis type 1: psychiatric disorders and quality of life impairment, Presse Med 2006; 35(2 Pt 2):277-80*
5. *Bogadi M, Kaštelan S, Bakija I, Kasun B, Psychiatric disorders in patients with neurofibromatosis. Libri Oncologici: Croatian Journal of Oncology 2018; 46:106-112*
6. *Bujas Petković Z. I. Dio Dijagnoza i procjena. In: Bujas Petković Z, Frey Škrinjar J et al. Poremećaji autističnog spektra. Zagreb:Šk. knjiga; 2010. p.6-81*
7. *Chisholm AK, Anderson VA, Pride NA, Malarbi S, North KN, Payne JM. Social Function and Autism Spectrum Disorder in Children and Adults with Neurofibromatosis Type 1: a Systematic Review and Meta-Analysis. Neuropsychol Rev 2018; 28:317-340*
8. *Cipolletta S & Spina G, Spoto A. Psychosocial functioning, self-image, and quality of life in children and adolescents with neurofibromatosis type 1. Child Care Health Dev 2018; 44:260-268*
9. *Cohen R & Shuper A, Developmental manifestation in children with neurofibromatosis type 1, Harefuah 2010; 149:49-52, 61*
10. *Cohen JS, Levy HP, Sloan J, Dariotis J, Biesecker BB, Depression among adults with neurofibromatosis type 1: prevalence and impact on quality of life, Clin Genet 2015; 88:425-30*
11. *DeFries JC, Vandenberg SG, McClearn GE. Genetics of specific cognitive abilities. Annu Rev Genet 1976; 10:179-207*
12. *Domon-Archambault V, Gagnon L, Benoît A, Perreault S, Psychosocial Features of Neurofibromatosis Type 1 in Children and Adolescents, J Child Neurol 2018; 33:225-232*
13. *Eijk S, Mous SE, Dieleman GC, Dierckx B, Rietman AB, de Nijs PFA, Ten Hoopen LW, van Minkelen R, Elgersma Y, Catsman-Berrevoets CE, Oostenbrink R, Legerstee JS. Autism Spectrum Disorder in an Unselected Cohort of Children with Neurofibromatosis Type 1 (NF1). J Autism Dev Disord. 2018; 48:2278-2285*
14. *Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM, Lalloo F. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 2010; 152A:327-32*
15. *Fekih-Romdhane F, Othman S, Sahnoun C, Helayem S, Abbes Z, Bouden A, [Anksiozni poremećaji kod tipa 1 neurofibromatoze: prikaz slučaja], Arch Pediatr 2015; 22:956-60*
16. *Garcia-Penas JJ, Learning disorders in neurofibromatosis type 1, Rev Neurol 2017; 64(s01):S59-S63*
17. *Garg S, Plasschaert E, Descheemaeker M-J, Huson S, Borghgraef M, Vogels A, Gareth Evans D, Legius E, Green J, Autism spectrum disorder profile in neurofibromatosis type I, J Autism Dev Disord 2015; 45:1649-57*
18. *Huguen J, Audebert-Bellanger S, Brenaut E, Misery L, Abasq-Thomas C, Post-traumatic Stress Disorder in Patients and Relatives Following a Diagnosis of De novo Neurofibromatosis Type 1, Acta Derm Venereol 2018; 98:291-293*
19. *Huson SM. Recent developments in the diagnosis and management of neurofibromatosis. Arch Dis Child 1989; 64:745–749*
20. *Hyman SL, Shores EA, North KN. The nature and frequency of cognitive deficites in children with neurofibromatosis type 1. Neurology 2005; 65:1037-44*
21. *Hyman SL, Shores EA, North KN. Learning disabilities in children with neurofibromatosis type 1: subtypes, cognitive profile and attention-deficit-hyperactivity disorder. Med child Neurol 2006; 48:973-7*
22. *Juretić Z & Škevin V. Hiperaktivni poremećaj (ADHD). In: Nikolić S, Marangunić M, et al. Dječja i adolescentna psihijatrija. Zagreb: Šk. knjiga; 2004. p 111*
23. *Koth CW, Cutting LE, Denckla MB. The association of neurofibromatosis type 1 and attention deficite hyperactivity disorder. Child Neuropsychol 2000; 6:185-194*
24. *Lehtonen A, Howie E, Trump D, et al. Behaviour in children with neurofibromatosis type 1: cognition, executive function, attention, emotion, and social competence. Dev Med Child Neurol 2013; 55:111-25*
25. *Leschziner GD, Golding JF, Ferner RE, Sleep disturbance as part of the neurofibromatosis type 1 phenotype in adults, Am J Med Genet A 2013; 161A:1319-22*
26. *Lewis AK, Porter MA, Williams TA, Bzishvili S, North KN, Payne JM. Attention to faces in social context in children with neurofibromatosis type 1. Dev Med Child Neurol, 2018*
27. *Lidzba K, Grandstrom S, Lindenau J, Mautner VF. The adverse influence of attention-deficit disorder with or without hyperactivity on cognition in neurofibromatosis type 1. Dev Med Child Neurol 2012; 54:892-897*
28. *Maraña Pérez AI and co-workers Duat Rodríguez A, Soto Insuga V, Domínguez Carral J, Puertas Martín V, González Gutiérrez Solana L, Prevalence of sleep disorders in patients with neurofibromatosis type 1, Neurologia 2015; 30:561-5. doi:10.1016/j.nrl.2014.04.015. Epub 2014 Jun 26*
29. *Martin S, Wolters P, Baldwin A, Gillespie A, Dombi E, Walker K, Widemann B, Social-emotional functioning of children and adolescents with neurofibromatosis type 1 and plexiform neurofibromas: relationships with cognitive, disease, and environmental variables. J Pediatr Psychol 2012; 37:713-24*
30. *Mirza T & Majeed MH. Neurofibromatosis and psychosis: coincidence or co-occurrence? Aust N Z J Psychiatry 2018:4867418818360*
31. *Molosh AI & Shekhar A. Neurofibromatosis type 1 as a model system to study molecular mechanisms of autism spectrum disorder symptoms. Prog Brain Res 2018; 241:37-62*
32. *Payne JM, Barton B, Shores EA, et al. Paired associate learning in children with neurofibromatosis type1: Implications for clinical trials. J Neurol 2013; 260:214-20*
33. *Payne JM, Arnold SS, Pride NA, North KN, Does attention-deficit-hyperactivity disorder exacerbate executive dysfunction in children with neurofibromatosis type 1?, Dev Med Child Neurol 2012; 54:898-904*
34. *Pierpont EI, Hudock RL, Foy AM, Semrud-Clikeman M, Pierpont ME, Berry SA, Shanley R, Rubin N, Sommer K, Moertel CL. Social skills in children with RASopathies: a comparison of Noonan syndrome and neurofibromatosis type 1. J Neurodev Disord 2018; 10:21*
35. *Pride NA, Barton B, Hutchins P, Coghill DR, Korgaonkar MS, Hearps SJC, Rouel M, Malarbi S, North KN, Payne JM. Effects of methylphenidate on cognition and behaviour in children with neurofibromatosis type 1: a study protocol for a randomised placebo-controlled crossover trial. BMJ Open 2018; 8*

36. *Pride NA, Payne JM, North KN, The impact of ADHD on the cognitive and academic functioning of children with NF1. Dev Neuropsychol 2012; 37:590-600*
37. *Samuelsson B & Riccardi VM, Neurofibromatosis in Gothenburg, Sweden. III. Psychiatric and social aspects, Neurofibromatosis 1989a; 2:84-106*
38. *Samuelsson B & Riccardi VM. Neurofibromatosis in Gothenburg, Sweden. II. Intellectual compromise. Neurofibromatosis 1989b; 2:78-83*
39. *Samuelsson B & Samuelsson S. Neurofibromatosis in Gothenburg, Sweden. I. Background, study design and epidemiology. Neurofibromatosis 1989c; 2:6-22*
40. *Sanchez-Marco SB, Lopez-Pison J, Serrano-Vinuales I, Troyas-Fernandez de Garayalde L, Lafuente-Hidalgo M, Monge-Galindo L. Neurofibromatosis type 1 and attention-deficit disorder. Our current experience. Rev Neurol 2019; 68:7-10*
41. *Thukral-Mahajan P, Shah N, Kalra G, Andrade C4. Electroconvulsive therapy for medication-refractory depression in a patient with ruptured intracranial dermoid cyst, meningioma, and neurofibromatosis. Indian J Psychiatry 2017; 59:493-495*
42. *Walsh KS, Vélez JI, Kardel PG, Imas DM, Muenke M, Packer RJ, Castellanos FX, Acosta MT, Symptomatology of autism spectrum disorder in a population with neurofibromatosis type 1, Dev Med Child Neurol 2013; 55:131-8*
43. *Zöller ME & Rembeck B, A psychiatric 12-year follow-up of adult patients with neurofibromatosis type 1, J Psychiatr Res 1999; 33:63-8*
44. *Zöller ME, Rembeck B, Bäckman L: Neuropsychological deficits in adults with neurofibromatosis type, Acta Neurol Scand 1997; 95:225-32*

*Correspondence:*
*Marija Bogadi, MD*
*Psychiatry Hospital for Children and Adolescents*
*Ivana Kukuljevića 11, 10 000 Zagreb, Croatia*
*E-mail: marija.bogadi@gmail.com*