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Nesreen K yasien, Mohamed A Abdraboh[1], Mohammed Al-haggar[2], Nehad Nasef[3], Mohamed A El-Missiry[1]

[1]Zoology Department, Faculty of Science, Mansoura University, Egypt

[2]Genetics unit, Department of pediatrics, Faculty of medicine, Mansoura University, Egypt

[3]Neonatal intensive care unit, Faculty of medicine, Mansoura University children hospital, Egypt

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Original Article

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Nesreen K yasien, Mohamed A Abdraboh[1], Mohammed Al-haggar[2], Nehad Nasef[3], Mohamed A El-Missiry[1]

1Zoology Department, Faculty of Science, Mansoura University, Egypt

2Genetics unit, Department of pediatrics, Faculty of medicine, Mansoura University, Egypt

3Neonatal intensive care unit, Faculty of medicine, Mansoura University children hospital, Egypt

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Abstract

There are no data on long-term safety for the use of melatonin. Since Down syndrome children show low levels of melatonin, it is anticipated that exogenous treatment with melatonin could be caring. The present study aimed to investigate the safety of melatonin treatment in Down syndrome children. The following children were recruited; children with Down syndrome, Children with down syndrome and treated with 1 mg/day melatonin and Down syndrome children treated with melatonin then melatonin was withdrawn for 18 months. Age matched ten healthy children attending for phlebotomy or day case procedures and whose results were subsequently normal. Biomarkers of liver functions, kidney function, and levels of cholesterol and triglycerides were estimated in serum. After melatonin supplementation, there were insignificant changes in the levels of glutamic pyruvic transaminase (GPT), glutamic oxalacetic transaminase (GOT), creatinine, urea, cholesterol, triglycerides levels. In conclusion, the daily administration with melatonin for six months is safe on liver and kidney functions and the levels of cholesterol, triglycerides.

1. Introduction

Down syndrome (DS) is a chromosomal abnormality arising from the triplicated copy of chromosome 21 (Trisomy 21) and this disease was evaluated to influence 1 out of 750 live births (Perkins, 2017). DS related pathological features are a direct result of excessive expression of chromosome 21 allocated gene of superoxide dismutase (SOD). It is found in DS 50% greater level due to gene dosage effect. The highly activity of the SOD in DS children caused oxidative damage via increasing accumulation of hydrogen peroxide level. Oxidative stress (OS) during developmental growth may injure many fetal organs and tissues including neurodegeneration and its related pathology of early Alzheimer's disease (AD) onset, (Meguid et al., 2010).

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone that is produced mainly by the pineal gland (Omar and Saba, 2010). Melatonin regulates a variety of physiologic functions, such as circadian rhythm, immune regulation, prooxidant and antioxidant activity, and neuroprotection (Marra et al., 2019). Melatonin secreted under the influence of light/dark cycle in human and other vertebrates. Melatonin has a role in the regulation of circadian rhythms, modulation of the immune response and hormone release, and minimize radical burden inside tissues (Jaworek et al., 2017). Melatonin has direct neutralizing mechanism to reactive radicals, and indirect effect through modulation of antioxidant enzymes (Reiter et al., 2016). Children with DS showed a reduction in the plasma concentration of melatonin resulting in an increased oxidative risk for DS children (Uberos et al., 2010). Many reports showed potential evidence of efficacy and safety of melatonin therapy in children and others explain no toxicological chronic melatonin treatment (Seabra et al., 2000); (Gitto et al., 2012).

There are no data on long-term safety for the use of melatonin, assuming long term means 6 months or more of daily medication. Since Down syndrome children show low levels of melatonin, it is anticipated that exogenous treatment with melatonin could be caring. The present study aimed to investigate the safety of melatonin treatment in Down syndrome children.

2. Subjects and Methods

This study was approved by the Ethics Committees of faculty of science, Mansoura University, Egypt. All families and participants received verbal and documented information on the

study and written consent was obtained prior to recruitment.

The following children were recruited: (a) children with Down syndrome, (b) Children with down syndrome and treated with melatonin and (c) down syndrome children treated with melatonin then melatonin was withdrawn for 18 months. All down syndrome children were attending the multidisciplinary Down syndrome clinic in children hospital at Mansoura University. Finally (e) age matched 10 healthy children attending for phlebotomy or day case procedures and whose results were subsequently normal. Children in both groups were excluded if they had recent fever or evidence of infection. DS children received 1mg melatonin per day of melatonin orally.

2 ml blood samples were taken from antecubital vein in chilled tubes without anticoagulant for each patient subject to treatment. The blood samples were centrifuged at 1500 xg for 10 min to separate blood cells from serum. The serum used for determination of biochemical parameters. These biochemical parameters were evaluated in the blood of DS patients before treatment, then 3 and 6 months after treatment. After melatonin withdrawal for 18 month and compared to normal children was determined.

The levels of albumin, total protein, glutamic pyruvic transaminase (GPT), glutamic oxalacetic transaminase (GOT), were measured in serum according to (Bakker and Mücke, 2007) by automated response 920 with the guidance kit of Diasys that was brought from (Holzheim, Germany). The levels of these parameter was expressed as mg/dl.

The levels of albumin, total protein, alanine amino transferase (GPT) and aspartate amino transferase (GOT) were measured in serum according to (Bakker and Mücke, 2007) by automated response 920 with the guidance kit of Diasys that was brought from (Holzheim, Germany). The levels of these parameters were expressed as mg/dl and U/L respectively

The levels of creatinine, urea and uric acid were measured in serum according to (Bakker and Mücke, 2007) by automated response 920 with the guidance kit of Diasys that was brought from (Holzheim, Germany). The levels of these parameter were expressed as mg/dl.

The levels of cholesterol, triglyceride was measured in serum according to (Bakker and Mücke, 2007) by automated response 920 with the guidance kit of Diasys that was brought from (Holzheim, Germany). The levels of these parameters were expressed as mg/dl.

Statistical analysis:

Data were subjected to statistical analysis using the statistical software program Prism (GraphPad, Prism, 6.01). Means and the standard error of the mean (±SEM) n = 25 for each variable were estimated. Differences between means of different groups were evaluated using one-way ANOVA.

3. Results

Age and body mass index in Down syndrome children during six months of treatment with I mg/day melatonin and after withdrawal terminating the treatment after 18 months.

Table (1): Age and body mass index in Down syndrome children during six months of treatment with melatonin.

Month		Normal children	DS children			
			MLT			
			0	3	6	Withdrawal
AGE(MONTH)	Mean	12	8.5	11.5	14.5	32.5
	±SEM	± 0.5	± 0.3	± 0.3	± 0.3	± 0.3
BMI (KG/M2)	Mean	18.8	17.3	17.4	18.5	19.4
	±SEM	± 0.7	± 0.5	± 0.3	± 0.6	± 0.8

The treatment of DS children with 1mg/day melatonin showed values of liver function parameters (Glutamic pyruvic Transaminase (GPT), glutamic oxalacetic transaminase (GOT), albumin, total protein levels) within the normal ranges of normal children (Table 2). The withdrawal of melatonin did not affect liver function parameters after 18 months of withdrawal.

Table 2: Prevalence of GPT, GOT, albumin and total protein (U/L) &(mg/dL) levels in serum of DS children during six months of treatment.

Month		Normal children	DS children				Normal Range
			MLT				
		Control	0	3	6	withdrawal	
GPT	Mean	20.9	11.8	13	15	21	<30
	±SEM	±1.6	± 1.7	± 2.7	± 4.1	± 3.5	U/L
GOT	Mean	27.2	14.8	15	22	28	<50
	±SEM	±3	± 2.4	± 3.1	± 3.1	± 2.4	U/L
Total protein	Mean	7.48	6.9	7.5	7.6	7.6	5.7-8.0
	±SEM	±0.22	± 0.19	± 0.18	± 0.3	± 0.2	Mg/dl
Albumin	Mean	4.3	4.6	5.1	5.2	4.4	3.5-5.2
	±SEM	±0.12	± 0.2	±0.4	±0.4	± 0.24	Mg/dl

The present study also assayed kidney function parameters including uric acid, creatinine and urea in children with Down syndrome compared with normal range of healthy children. The data showed normal value of kidney function in DS children during treatment with melatonin as compared to normal children (Table 3). The withdrawal of melatonin did not affect kidney function parameters.

The treatment of DS children with 1mg/day melatonin showed values of cholesterol and triglycerides in serum within the normal ranges of normal children (Table 2). The withdrawal of melatonin did not affect these parameters after 18 months of withdrawal.

Table (3): Levels of uric acid, creatinine and urea (mg/dL) in serum of DS children during six months of treatment with melatonin.

Month		Normal children	DS children				Normal Range
				MLT		withdrawal	
			0	3	6		
Uric acid	Mean	3.0	2.7	2.6	2.4	3.4	1.8-5.0 mg/dl
	±SEM	±0.31	± 0.39	±0.4	±0.4	±0.89	
Creatinine	Mean	0.54	0.57	0.60	0.51	0.52	0.5-1.2
	±SEM	±0.05	±0.067	±0.09	±0.064	±0.057	mg/dl
Urea	Mean	27.7	27.14	30.6	32.7	33	11-36
	±SEM	±3.8	±2.9	±3.4	±3.3	±4.2	Mg/dl

Table (4): Levels of cholesterol and triglyceride (mg/dL) in serum of DS children during six months of treatment.

Month		Normal children	DS children				Normal range
				MLT		Withdrawal	
			0	3	6		
Cholesterol	Mean	141	168.7	180.7	178.7	167.8	< 200mg/dl
	±SEM	± 8.5	± 14.1	± 11.7	± 11.6	± 17.5	
Triglycerides	Mean	131	147.5	137	103	97	< 200mg/dl
	±SEM	±7.1	±16.4	±7.9	±15.1	±3.7	

4. Discussion

Many clinical trials give an evidence that exogenous melatonin has protective effects in avoidance of cell damage in body circumstances, such as sepsis, chronic metabolic disease, asphyxia, inflammation, and lung cancer (Eghbal et al., 2016). The level of melatonin in children with DS is extremely reduced when compared to age-matched controls, resulting in increased reactive species and oxidative risk in their organs (Uberos et al., 2010), (Vacca et al., 2019).

Studies of melatonin treatment for children with developmental disabilities provide mounting evidence of its efficacy and safety. Melatonin is commonly recommended to treat sleep problems in children with developmental disabilities (Schwichtenberg and Malow, 2015). However, few studies document the efficacy and safety of melatonin in Down syndrome children. Children with Down syndrome often have a weakened immune system, and as a result are especially vulnerable to infection. By middle age, they appear to be years older than their chronological age, and they are prone to develop some of the diseases associated with aging, such as osteoporosis and premature senile dementia.

Melatonin can be safe and effective in treating pediatric sleep disturbances including both sleep disorders and the sleep disorders associated with various neurological conditions(Esposito et al., 2019). It is also reported that patients with nonalcoholic steatohepatitis (NASH) were administered melatonin at a dose of 10 mg for 3 months. The follow-up after 3 months revealed the decrease in the level of liver enzymes. Similarly, Cichoz-Lach et al used the same regime and they also found the decreased level of liver enzymes and triglycerides and proinflammatory cytokines (Cichoz-Lach et al., 2010) . In another study a single melatonin dose of 50–100 mg/ was injected for the regulation of inflammatory and metabolic disorders (Cardinali and Hardeland, 2017). The same high doses of melatonin were administered preoperative single dose of melatonin in patients undergoing major liver resection and showed good tolerability. This positive impact on the postoperative condition was demonstrated by faster drop in GOT and GPT compared to placebo (Schemmer et al., 2008),(Nickkholgh et al., 2011),(Chojnacki et al., 2017). Statins are medications for regulating lipid metabolism and taken chronically and therefore hepatoprotective factors should be used on long-term basis and should be free of side effects. Recent report confirm that melatonin satisfies such conditions and displayed a significant hepatoprotective effect in patients treated with statins (Nickkholgh et al., 2011).

Accumulating evidence has suggested that individuals with chronic kidney disease (CKD) or on dialysis exhibit altered circadian rhythms of melatonin levels in the blood, and the production of melatonin is decreased with the progression of CKD to end-stage renal disease (ESRD)(Nicholl et al., 2014). In numerous experimental animal models of CKD and clinical settings, the effects of melatonin have been obvious on the improvement of renal function and lowering of blood pressure, accompanied by the normalization of circadian rhythms (Rahman et al., 2019). The present data confirm these studies and showed an insignificant effect on liver and kidney function in children with Down syndrome. The current study demonstrated values with normal ranges of the specific parameters of liver and kidney functions. The safety of long term intake of melatonin is attributed to the pleiotropic effects of melatonin comprising the consequences of numerous complementary interconnecting mechanisms, including the reduction of oxidative stress, inflammation and fibrosis. The present results also demonstrated an insignificant effect of melatonin administration on cholesterol and triglycerides in Down syndrome children compared and showed values with normal ranges. However, triglycerides showed lower values than DS patients even after withdrawal of melatonin treatment.

In conclusion, the daily administration with melatonin for six months is safe on liver and kidney functions and the levels of cholesterol, triglycerides.

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