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Manganese exposure: cognitive, motor and behavioral effects on children: a review of recent findings

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Abstract

Purpose of review—Manganese (Mn) is an essential element, but can be neurotoxic when exceeding the homeostatic range. We reviewed the most recent human studies (from January 2011 to July 2012) regarding the association between Mn exposure and cognitive, motor and behavioral effects on children.

Recent findings—A total of 10 articles were located; data were collected from five different countries. Six studies showed adverse effect of Mn on cognitive function. The most adopted cognitive test was the Wechsler Intelligence Scale for Children (WISC) or some subtests from it and results suggest an inverse association of higher Mn exposure with lower intellligence quotient. Three studies focused on motor effects of Mn; two of them found a direct association of higher Mn exposure with increased motor impairment. Two studies assessed Mn impact on behavior; one of them showed a correlation between higher Mn in water and both internalizing and externalizing behavioral scores. Potential limitations of these studies included the lack of validated biomarkers and the lack of consideration of mixed co-exposure with other neurotoxic agents.

Summary—Despite some potential limitations of the reviewed studies, the adverse effects of manganese exposure on the developing brain is well demonstrated and preventive strategies should be promoted.

Keywords

children; manganese; neurotoxicity

INTRODUCTION

Manganese (Mn) is an essential element, but can be neurotoxic when exceeding the homeostatic range. Despite lower levels of exposure, several studies showed cognitive and

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There are no conflicts of interest.

neurobehavioral implications in children [1–4]. Fewer studies focused on motor effects in children environmentally exposed to manganese. We reviewed the most recent studies assessing the impact of Mn exposure on cognitive, motor and behavioral functions in children.

METHODOLOGY

A systematic review of the scientific literature was conducted with PubMed, for the period from 1 January 2011 to 29 July 2012. The keywords used for the search were: manganese, child, children, adolescents, neurotoxicity, neuropsychological effects, cognition, IQ, motor, behavior, attention deficit hyperactivity disorder (ADHD), hyperactivity. We limited the search to full-length articles published in English. After reviewing the abstracts, we selected the studies pertaining to the review and focusing on motor, cognitive or behavioral functions in children. We found 10 articles published in the cited search period regarding studies on children from five different countries. Our review considered only the results from test/ questionnaires administered to the children, not to the mothers or other caregivers.

RESULTS

The main characteristics of the reviewed studies are reported in Table 1: country, type of study design, population size and age, the exposure biomarker or indicator, test/ questionnaire administered and main findings. We summarized the findings in three categories: cognitive, motor and behavioral.

Cognitive effects

Bouchard *et al.* [5] investigated the relation between Mn exposure through drinking water and intellligence quotient (IQ). They evaluated 362 children, aged 6–13 years, living in eight municipalities located on a gradient of Mn in water (MnW). Manganese was measured in residential tap water and in children's hair (MnH). With regard to the relationship between MnW and IQ in the adjusted model (for maternal intelligence, family income, and other potential confounders), the study showed that higher MnW was significantly associated with lower performance, verbal, and full scale IQ scores, with a difference of 6.2 points in IQ between children in the lowest and in the highest MnW quintiles. Considering MnH, in adjusted analyses, higher MnH was associated with lower full scale IQ scores. Moreover, the authors found that Mn intake from water, but not from diet, was significantly associated with MnH, suggesting that Mn exposure from water is metabolized differently from Mn ingested from diet.

Menezes-Filho *et al.* [6] investigated the relation between Mn in hair and blood (MnB), and blood lead (PbB), with children's IQ. They evaluated 83 children, aged 6–12 years, living near a ferromanganese plant in Brazil. Results showed that children's MnH (not MnB) was inversely associated with verbal and total IQ.

Other reviewed studies focused also on exposure to other metals, in addition to manganese.

Wasserman *et al.* [7] assessed the impact of arsenic (As) and manganese exposure on children's intellectual functions. The study population was composed of 299 children (8–11 years old), living in Bangladesh, a country with widespread contamination of well water with As and Mn. The design of the study stratified on As and Mn concentrations in domestic well water. Results showed that, when adjusted only for each other, MnB and arsenic in blood (AsB) were significantly and negatively related to most Wechsler Intelligence Scale for Children (WISC)-IV subscales. After further adjustment for sociodemographic variables and ferritin they observed an inverse association between MnB and perceptual reasoning and working memory from WISC.

Khan *et al.* [8] considered also the potential interaction between Mn and As and their effect on children's academic achievement in a study also conducted in Bangladesh. They considered a population of 840 children, aged 8–11 years, from Bangladesh, collecting data on well water samples from each child's house, on urinary As (UAs) measurement, and on academic achievement in three disciplines (Bangla, English, Mathematics). They found a significant inverse association between MnW and mathematics scores, also in adjusted model. The relation between MnW and language scores was not significant. The As biomarkers (As in urine and As in water) were not associated with any of the three disciplines' test scores.

Mn–Pb interaction in early childhood and its possible association with neurodevelopment deficiencies was investigated by Clauss Henn *et al.* [9]. They considered a population of 455 children from Mexico City, assessing infant/toddler neurodevelopment at 12, 18, 24, 30, and 36 months of age through the Bayley Scales (BSID-IIS). As regards exposure index, they measured Mn and Pb in whole blood. Results indicated that a mixed exposure to Mn and Pb has a greater impact on mental and psychomotor development than exposure to one of the two metals alone. Mixed-effect models showed a significant interaction over time.

Also, Lucchini *et al.* [10] examined the impact of Mn and Pb exposure cross-sectionally on cognitive function in early adolescence. The study analyzed the IQ in 299 adolescents (11–14 years old), environmentally exposed to Mn and Pb, considering, as biomarkers, manganese in blood and hair, and lead in blood. Results demonstrated a significant adverse effect of lead on cognitive functions, with a reduction, after controlling the confounders, of about 2.4 IQ points in the IQ score for a two-fold increase of the PbB. No manganese effect on cognitive function was observed, nor was an interaction with Pb exposure found.

Effects on motor functions

In the study by Lucchini *et al.* [11] several tests were used to assess motor impairment related to manganese exposure: Luria Nebraska Motor Battery, Finger Tapping, Visual Simple Reaction Time, Pursuit Aiming, Tremor Test, and Body Sway. Regression model showed a significant impairment of motor coordination (Luria-Nebraska test, $P = 0.0005$), hand dexterity (Pursuit Aiming, $P = 0.0115$) and odor identification (Sniffin' task, $P = 0.003$) associated with soil Mn. Tremor intensity was directly associated with blood ($P = 0.005$) and hair ($P = 0.01$) Mn concentrations.

Hernández-Bonilla *et al.* [12] assessed the association between Mn exposure and motor function in 195 children (100 exposed and 95 not exposed), aged 7–11 years old, living in Mexico, near a Mn plant. To assess motor functions, they administered three tests: the Grooved Pegboard, the Finger Tapping, and the Santa Ana Test. Comparing exposed and not-exposed groups, the authors observed a significant difference in the number of errors on the Grooved Pegboard (those with Mn exposure more frequently made errors during the test); no differences were observed between groups in the other two motor tests. Regarding the association between biomarkers of Mn exposure and motor functions, they found an inverse association between MnB and the fingertapping performance for each hand. No associations were found between MnB and Santa Ana and Grooved Pegboard, or with MnH.

The effects of arsenic and manganese ingestion, through drinking water, on children's motor functions were further studied by Parvez *et al.* [13]. They investigated the association of WAs and WMn with motor function in a population of 304 children (8–11 years) from Bangladesh. They assessed motor functions using the Briuninks-Oretetsky test, generating a summary score (total motor composite, TMC) and four subscales: fine manual control (FMC), manual coordination, body coordination, strength and agility. Adjusted model found an inverse association between AsB and three motor scales: TMC, FMC and BC. No associations were found between MnB or PbB and motor function.

Behavioral effects

Two recent studies analyzed the correlation between manganese exposure and behavior in children. Khan *et al.* [14] investigated the association of Mn and As in well water with classroom behavior among 201 Bangladeshi children, aged 8–11 years. Teachers of the recruited children filled out a questionnaire (Child behavior checklist-teacher's report form), in which they rated a range of children's behaviors and problems, like internalizing behavior (anxious/depressed, refuse to talk) and externalizing behavior (e.g. attention problem, aggressiveness). Results showed a significant and positive association between WMn and both internalizing and externalizing behavioral scores, with the strongest relation between WMn and externalizing problems.

Also Lucchini *et al.* [10] examined adolescents' behavior, administering the Conners-Wells Adolescent Self-Report Scale-Long Form (CASS:L), composed of 87 items, assessing 10 domains. The regression analysis was also conducted using the 10 subscales of CASS:L as dependent variable and showed a marginal association only between BPb and the ADHD subscale (P =0.069).

CONCLUSION

The reviewed studies suggest that Mn exposure is related to cognitive, motor and behavior deficits in children. Six recent studies [5–10] found an adverse effect of Mn on cognitive function. The most used cognitive test was the WISC or some subtests from it, and overall the results suggest an inverse association between Mn exposure and IQ [1,2,4]. Although these studies showed inverse relationships between cognitive performance and Mn, results are difficult to compare as the cognitive tests administered were different, the source of Mn was different (ambient vs. oral) and the cultural/economic backgrounds of the populations varied widely. The studies included were all epidemiologic and did not consider the mechanism involved in cognitive impairment due to Mn exposure. As we focused on human studies without access to neurotissue, we believe mechanism was outside the scope of the review. One study found an association between Pb and IQ, and not between Mn and IQ [11].

Three studies [11–13] focused on motor effects of Mn; two of them [11–12] found a positive association. Lucchini *et al.* [11] found a significant impairment in Luria-Nebraska test, Pursuit Aiming and Sniffin' test associated with soil Mn, whereas tremor intensity was positively associated with MnB and MnH; Hernández-Bonilla *et al.* [12] showed an inverse association between MnB and the execution of the Finger Tapping test. Very few studies focused on the effects of Mn on children's motor skills, although data on motor effects in adults, occupationally [15–17] or environmentally [18–20] exposed to Mn, are reported, as well in animal studies.

Two studies [10,14] assessed the impact of Mn on behavior; only one [14] showed a correlation between WMn and internalizing and externalizing behavior scores. The correlation between Mn and hyperactive behavior is probably due to the dopaminergic and gamma-aminobutyric acidergic systems, which have a role in hyper-activity in children and are also vulnerable to Mn [21,22].

The studies here reviewed have several limitations: one difficulty is the lack of a validated biomarker of exposure or exposure index for Mn. Manganese in water is the most used exposure index, but is not a marker of internal dose; Mn in blood or hair is the most frequent biomarker of internal dose, but each has limited correlation with external environment indices. Another potential limitation in studies regarding Mn exposure is the lack of attention to mixed exposure: most studies focus on a single agent of exposure and do not measure or adjust for potential effects of other chemicals. Finally, the 'geographic generalizability' could represent a limitation, due to the difficulty in comparing some countries (for example, Bangladesh) with urban communities (socioeconomic and demographic characteristics could differ between children living in different countries).

Despite these limitations, we believe adverse effects of manganese exposure on children are well demonstrated by these studies and demonstrate an overall consistency in results. A previous review, considering 12 studies, published between 1977 and 2007, also supported the evidence of cognitive and behavioural effects related to pediatric Mn exposure [23▪]. Based on this knowledge, preventive strategies to reduce Mn exposure and further investigations on mixed exposure and the role of genetic factors should be promoted.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

▪ of special interest

▪ ▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 283).

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KEY POINTS

- Mn is an essential element, but when exposure levels are high it can become neurotoxic.
- Despite lower levels of exposure when compared with occupational studies, several studies showed cognitive and neurobehavioral deficits in children; however, only a few studies focused on motor effects.
- Overall, the reviewed studies suggest that Mn exposure is related to cognitive, motor and behavior deficits in children.

Table 1

Characteristics of the reviewed studies (published between 2011 and 2012) on the relation between children's exposure to manganese and cognitive, motor and behavioral effects

Study	Country	Design	*N*	Age	Exposure indicator/ biomarker	Test/questionnaire	Main findings
Bouchard *et al.* [5]	Canada	Cross-sectional	362	6–13 years	WMn, MnH	Wechsler Abbreviated Scale of Intelligence (WASI)	A 10-fold increase in MnW was associated with a decrease of 2.4 IQ points, adjusting for maternal intelligence, family income, and other potential confounders. There was a 6.2-point difference in IQ between children in the lowest and highest MnW quintiles; MnW was more strongly associated with performance IQ than verbal IQ.
Menezes-Filho *et al.* [6]	Brazil	Cross-sectional	83	6–12 years	MnH, MnB, PbB	WISC-III, HOME Inventory	MnH was negatively related to total and verbal IQ.
Wasserman *et al.* [7]	Bangladesh	Cross-sectional	299	8–11 years	WMn, WAs	A battery of WISC-IV subtest, HOME Inventory	When adjusted for each other, As and Mn in whole blood were significantly negatively related to most WISC scores. After adjustment with ferritin and sociodemographic variables, MnB remained associated with perceptual reasoning and working memory scores.
Khan *et al.* [8]	Bangladesh	Cross-sectional	201	8–11 years	WMn, UAs, MnB, PbB	Child behavior checklist-teacher's report form (CBCL-TRF)	WMn was positively and significantly associated with internalizing, externalizing, and total scores of the questionnaire filled out by teachers.
Clauss Henn *et al.* [9]	Mexico	Longitudinal	455	12–36 months	MnB, PbB	Bayley scales of infant development-II, Spanish version (BSID-II)	Mixed effects models showed a significant interaction over time: highest manganese quintile × continuous lead; mental development score, psychomotor development score, slopes for the estimated 12-month lead effect on 18-month mental development and 24-month through 36-month psychomotor development scores were steeper for children with high Mn than for children with midrange Mn levels.
Lucchini *et al* [10]	Italy	Cross-sectional	299	11–14 years	MnB, PbB, MnH	WISC-III; Conners-Well's Adolescent Self-Report Scale (CASS:L)	According to a multiple regression model considering the effect of other covariates, a reduction of about 2.4 IQ points resulted from a two-fold increase of BPb. Manganese was not associated with cognitive and behavioral outcomes, nor was there any interaction with lead.
Lucchini *et al.* [11]	Italy	Cross-sectional	311	11–14 years	MnB, MnH, MnU	Luria-Nebraska Motor battery, Finger Tapping, Visual Simple Reaction Time, Pursuit Aiming, Tremor Test, Body Sway	Regression model showed significant impairment of motor coordination (Luria-Nebraska test), hand dexterity (Pursuit Aiming test) and odor identification

Study	Country	Design	*N*	Age	Exposure indicator/ biomarker	Test/questionnaire	Main findings
							(Sniffin' test) associated with soil manganese. Tremor intensity w (Sniffin' test) associated with soil manganese. Tremor intensity w (Sniffin' test) associated with soil manganese. Tremor intensity w *P* =0.005) and hair (*P* =0.01) manganese.
Hernández-Bonilla *et al.* [12]	Mexico	Cross-sectional	195	7–11 years	MnH, MnB	Grooved Pegboard, Finger Tapping Santa Ana Test	MnB showed an inverse association on the execution of the finger tapping test (*P* =0.02), but no association was observed with MnH.
Parvez *et al*. [13]	Bangladesh	Cross-sectional	304	8–11	WMn, WAs, UAs, MnU, AsB, MnB, PbB, SeB	Bruininks-Oseretsky test (BOT-2)	As exposure (AsB) was inversely associated with motor function scores (in particular with total motor composite and body coordination). Mn was not associated with motor functions.
Khan *et al.* [14]	Bangladesh	Cross-sectional	840	8–11 years	WMn, WAs	Academic achievement (annual scores): Bangla, English, Mathematics	WMn above 400 μg/l was associated with 6.4% score loss in mathematics test scores, not in Bangla and English

AsB, Arsenic in blood; MnB, manganese in blood; MnH, manganese in hair; MnU, manganese in urine; PbB, blood lead; SeB, selenium in blood; UAs, arsenic in urine; WAs, arsenic in water; WMn, manganese in water.