Review

B. Payá González
N. Fuentes Menchaca

Neurobiology of autism: neuropathology and neuroimaging studies

Programa de Salud Mental Infanto-Juvenil
C. H. Padre Menni
Santander (Spain)

Introduction. This study performs a review of the last studies in the field of neuropathology and neuroimaging of autism.

Method. A search was done in Medline for articles on neuropathology and neuroimaging in autism and the most relevant articles of the last 10 years up to date were selected.

Results. The existence of structural abnormalities in the brain of patients with autism, affecting different brain structures such as the cerebellum, limbic system, frontal and temporal cortexes, corpus callosum and basal ganglia seems to be demonstrated.

Conclusion. The alterations found with the neuroimaging techniques are identified in the different brain structures. At present, there is almost generalized thinking that brain alterations in autism are not limited to a single brain area but involve different structures within a globally affected neuronal network. Future studies will allow us to increase knowledge on this disorder's pathophysiology.

Palabras clave:
Autism. Neuropathology. Neuroimaging. Neurobiology.

Actas Esp Psiquiatr 2007;35(4):271-276

Neurobiología del autismo: estudio de neuropatología y neuroimagen

Introducción. El presente trabajo realiza una revisión de los últimos estudios en el campo de la neuropatología y neuroimagen del autismo.

Método. Búsqueda en Medline de los artículos de neuropatología y neuroimagen en autismo y selección de los artículos más relevantes de los últimos 10 años hasta la actualidad.

Resultados. Parece demostrada la existencia de anomalías estructurales en los cerebros de pacientes con autismo afectando a diversas estructuras cerebrales como el cerebelo, sistema límbico, cortezas frontal y temporal, cuerpo calloso y ganglios basales.

Conclusión. Las alteraciones encontradas con las técnicas de neuroimagen se identifican a nivel de diferentes estructuras cerebrales. Actualmente es una idea casi generalizada que las alteraciones cerebrales en el autismo no se reducen a una sola área cerebral, sino que envuelven a distintas estructuras dentro de una red neuronal globalmente afectada. Futuros estudios nos permitirán aumentar el conocimiento sobre la patofisiología de este trastorno.

Key words:
Autismo. Neuropatología. Neuroimagen. Neurobiología.

Correspondence:
Beatriz Payá González
CSM Infanto-Juvenil
Luis Vicente Velasco, 1
39011 Santander (Spain)
E-mail: hdtca@mennisant.com

INTRODUCTION

Autism is a neurodevelopment disorder characterized by both quantitative and qualitative disorders in speech and social communication and a stereotyped pattern in the individual's interests.

Neurobiological research has contributed to there being greater knowledge about the neuroanatomical bases of this clinical entity, with special contribution of structural and functional neuroimaging techniques.

In this article, after having reviewed the existing literature in this research field, we have tried to express to the most relevant findings of neuroimaging and neuropathology studies of autism.

The results of these studies have contributed to the present thinking that the clinical manifestations of autism correspond to brain alterations. However, neuropsychological and neuroimaging findings indicate that this does not involve only a singe structure or system altered in this entity, it being proposed that the primary defect could be in the brain cytoarchitecture, more specifically on the dendritic level.

STUDIES OF CEREBRAL NEUROPATHOLOGY

The first autopsies conducted in brains of subjects with autism detected a decrease of cerebellum purkinje cells[1,2]. Given that loss of purkinje cells is a known complication in

epilepsy and that the subjects analyzed were patients with epilepsy, the relevance of these cases was doubted.

For the first time, Ritvo et al. found a decrease in the number of purkinje cells in the vermix and cerebellar hemisphere of four patients with autism who did not suffer epilepsy[3]. The significant difference between the ages of the cases and controls in this study made it difficult to extrapolate the findings.

In 1991, Kemper and Bauman[4-6] conducted one of the most relevant studies on anatomical alterations in autism. They analyzed the brains of 6 autistic patients, finding the primary alterations in the limbic system, cerebellum, oliva inferior. These brains had no gross morphological alterations, however, a decrease in the size of neuronal cells and an increase in neuronal density in the cerebral amygdala and other structures of the limbic system were found in comparison with the brains of the control group.

The presence of densely distributed small neuronal cells is an anatomopathological pattern observed in early stages of brain maturation, suggesting a possible alteration of neuronal maturation in autism.

In all the brains analyzed by the authors, there was also a decrease of purkinje cells in the cerebellar cortex, which would suggest a congenital etiology.

Another interesting finding in these autopsies was the «age-related» changes in cell size and number in the oliva inferior and cerebellar nuclei. The changes observed with age suggest a process that began with neuronal hypertrophy in childhood and a progressive atrophy and neuronal loss in adult life.

Increase in brain weight is another finding characteristic of the neuropathology studies.

Bailey et al.[7] found greater weight in three of the four brains of autistic patients in comparison with weight observed in the brains of the general population. Histologically, there was no evidence of a decrease in neuronal density, considering that the weight increase could be at the expense of an increase in neuron number.

The type of alterations observed in the neuropathological studies point to a possible alteration in the prenatal stages of brain development that could continue in development until adult life[8]. Maturation alterations are also a finding observed in individuals with mental retardation. However, in these cases, on the contrary to autism, the most outstanding changes occur in the brain cortex.

The neuropathological alterations observed in the limbic system structures in subjects with autism could be translated into functional deficits in data acquisition and processing, leading to cognition, speech and social interaction disorders, all these observed among the symptoms of autism.

NEUROIMAGING STUDIES

Structural and functional neuroimaging techniques have helped to contribute greater consistency to the findings discovered on other research levels.

Considering the findings of the different neurobiological investigations together, one of the most proposed theories at present in autism is that of a possible alteration in neurodevelopment in different brain structures.

In structural neuroimaging studies, the finding that seems to be most specific in autism is increased brain volume. In a study with MRI, Filipek et al.[9] detected an increase in brain volume for the first time in subjects with autism compared with a control group who had speech development disorders. This finding was subsequently verified by other groups[10] who describe an increase in total brain volume, brain tissue and volume of lateral ventricles in subjects with autism.

After analyzing independent brain structures, Piven et al.[11] found that the increase in total brain volume occurred at the expense of the volume increase in temporal, parietal and occipital but not frontal lobes. Therefore, these authors propose that brain volume enlargement in autism does not affect all the brain structure but rather certain areas whose identification could have significant neurobiological implications.

Enlargement of brain volume seen with structural techniques is consistent with findings of neuropathological study and brain circumference[12,13]. On the other hand, similar studies performed with subjects having other development disorders could not identify an increase in brain volume between patient groups, pointing to the specificity of the finding.

Studies conducted with positron emission tomography (PET)[14,15] show a global pattern of brain metabolism increase in patients with autism, which could indirectly support the findings reported with structure techniques.

Although brain volume enlargement is one of the primary relevant findings in brain image studies, subsequent investigations have focused on identifying specific structures involved in this entity's pathophysiology. Some of the most involved structures include the cerebellum, limbic system and frontal lobe.

Cerebellum

Animal studies[16] suggest that the cerebellum could play a role in the regulation of emotions and thinking. This structure is involved in the perception and control process of timing that may be important for the representation of mental images and anticipation and in speech process-

ing[17,18]. The cerebellum has also been related with control of attention, specifically in the change of selective attention between different sensorial and motor modalities[19]. Another aspect in which this structure plays an important role is speed regulation, consistency and adequacy of mental and cognitive process and in the control and integration of information and motor and sensorial activity[20]. Authors such as Bauman and Kemper[21] discuss the role of the cerebellum in superior functions and suggest the possibility that deficits occur in emotions, behavior and learning secondary to cerebellar lesions.

Alterations in the cerebellum in subjects with autism were described by Courchesne et al.[22] who described a circumscribed hypoplasia in cerebellar vermal lobes VI and VII (neocerebellar) in subjects with autism.

Hashimoto et al.[23] subsequently replicate this same finding, but on the contrary to the Courchesne group, the hypoplasia was not circumscribed to the neocerebellum but included other cerebellar vermix lobe, brain medulla, pons and middle brain. This is a finding that points to the theory of involvement of different structures.

Contrary to these authors and using MRI in 35 patients with autism, Piven et al.[24] found a global increase of cerebellar volume with absence of abnormalities in the neocerebellum. The increase of cerebellar volume detected was in the same range as that found in a previous study[25] in the temporal, parietal and occipital lobe, thus suggesting the idea of a possible alteration in a neuronal network made up of different brain structures in autism.

The alterations in the cerebellar structures were subject to debate since the initial finding of cerebellar hypoplasia could not be replicated by other authors[26,27] and because the hypoplasia of this structure may appear in subjects with other neurogenetic syndromes and in children subjected to chemotherapy and radiotherapy, indicating the non-specificity of this finding[29,38].

After the controversy of this first hypothesis of cerebellar hypoplasia in autism, Courchesne et al. proposed the possible existence of two types of cerebellar patterns in subjects with autism, some would have hypoplasia and others cerebellar hyperplasia[30].

Limbic system

The first studies using pneumoencephalography conducted in the 1970's[31] described a dilation of the left horn of the lateral ventricle in the temporal lobe in subjects with autism, postulating the existence of a medial temporal lobe dysfunction underlying this dilation area.

Limbic structure dysfunction as cause of the symptoms observed in autism has been supported by different authors and confirmed in the data obtained in cerebral neuropathology studies[32,33] and in animal studies[34].

In spite of the importance given to the limbic structures in this disorder's pathogeny, studies with structural neuroimaging have failed to demonstrate alterations on this level[35]. However, the normality these structures show in structural techniques does not necessarily mean that their function or neuropathology remains intact since studies that combine functional and structural techniques have found functional alterations in different brain areas with normal magnetic resonances[36]. In fact, studies with positron emission tomography have been able to identify anterior cingulate gyrus volume and metabolism alterations in autistic subjects[37-41].

Frontal lobe

The possibility of frontal lobe alterations in autism has been proposed by several authors[42-45].

In a SPECT study, Zilbovicius[46] observed a frontal hypoperfusion pattern in a 3-4 year old sample of subjects with autism, similar to that of normal children at earlier ages. When another brain SPECT was performed in the same patient sample three years later, he observed normalization of the perfusion, a pattern equal to that observed in the control subjects appearing. These findings suggest the existence of a delay in postnatal maturation of the frontal lobe in autism. Delay in frontal maturation could cause functional alterations of this structure as a consequence and suggest an abnormal cortical activation or connection.

In some of the previously mentioned structural studies[11,35], it is interesting to mention that the frontal lobe was the only structure that conserved its volume intact within a brain that was globally increased in volume. This finding could mean that the frontal lobe, in relationship with the global size of the brain, is precisely the most abnormal structure.

In fact, the frontal alterations have been observed in studies of functional activation[47,48] that show decreases in the activation of the prefrontal cortex in subjects with Asperger's syndrome when they are subjected to tests that require the use of the theory of the mind, cognitive function that is supposed to be altered in subjects with autism[49].

A recent study[50] conducted with SPECT that measured the brain blood flow based on predominant symptoms in each subject verified alterations in perfusion in the prefrontal cortex and anterior cingulate gyrus in autistic subjects who had symptoms of alterations in communication and social interaction. In the subjects with a stereotyped pattern of interests predominating in their symptoms, perfusion alterations located in the right middle temporal lobe were observed. Thus, each one of these sites could have a different clinical meaning.

Corpus callosum

One of the points of interest of the study of this anatomical structure is found in the fact that the distribution of its fibers reflects topographical models of cortical regions[51]. In this way, certain cortical regions may be mapped with specific subregions of the corpus callosum[52,53], thus supplying information on what is occurring on upper cortical levels.

In general, the axons of the anterior cortical regions are projected into the anterior part of the corpus callosum and those of the posterior cortical regions are projected into the posterior part of the corpus callosum. The importance of these data is found in the fact that the study of the size of the corpus callosum can be extended to knowledge of the nature of the pattern of anteroposterior abnormality of the cortical regions observed in subjects with autism[54].

In 1995, in a study with MRI, Egaas, et al.[55] found a decrease in corpus callosum size that they interpreted as secondary to hypoplasia of parietal lobe. The same alterations in posterior regions of the corpus callosum are replicated by the Piven group[56] who, on the contrary to the previous group, observed an increase in volume in posterior brain structures on the cortical level in subjects with autism. Carefully analyzing this finding, it is observed how the direction that the abnormalities found in the corpus callosum follow, that is, decrease of volume in anteroposterior direction, follows the opposite pattern of the alterations of the cortical structures in which an increase in anteroposterior is observed in relationship to the frontal lobe that conserves a normal size. As an explanation to this fact, the authors proposed that the decrease in anteroposterior volume of the corpus callosum would be relative to the increased cortical volume produced at the cost of the non-neuronal tissue or by cortical neurons that do not project their axons to the corpus callosum. In conclusion, according to these authors, the differences found in the corpus callosum size would not be real but rather an effect produced by a greater cortical volume.

Basal ganglia

Although the interest of the studies on autism has not especially focused on these anatomical structure, Sears et al.[57] find alterations in the basal ganglia and increased volume of the caudate nucleus in a sample of 35 subjects with autism compared with normal controls in age, gender and IQ.

The size of the caudate nucleus in this sample was correlated with the presence of compulsions and rituals, difficulties with minor change, and complex motor mannerisms.

The same group of investigators replicated these results again in a second sample, suggesting that the caudate nucleus could form a part of an abnormal neural network in autism and could be involved in the ritualistic and repetitive behaviors observed in this disorder.

CONCLUSIONS

The main contribution of neuroimaging studies to the field of autism is the confirmation of the existence of abnormalities in these patients' brains. These alterations have been identified in different brain structures, which suggest that more than there being a single brain area affected, different structures within a hypothetical neuronal network whose limits and anatomical connections must still be defined would be involved. Recent studies also suggest the possibility that the altered structures were different based on the predominant symptoms in the patients.

Another line open in the study of autism is in regards to the alterations of the function type, among which abnormalities of the brain neurotransmission are included. There are authors[58] who have proposed alterations in the normal process of serotonin synthesis.

Functional neuroimaging studies to detect alterations in brain development, functional studies of cognitive stimulation and standardization of the methodological criteria will help to increase knowledge on the pathophysiology of this disorder in the future.

REFERENCES

1. Bauman ML. Histoanatomic observations of the brain in early infantile autism. Neurology 1985;35:886-74.
2. Williams RS, Hauser SL, Purpura DP, DeLong GR, Swisher CN. Autism and mental retardation: neuropathology studies performed in four retarded persons with autistic behavior. Arch Neurol 1980;37:749-53.
3. Ritvo ER, Freeman BJ, Scheibel AB, Duong T, Robinson H, Crithne D, et al. Lower Purkinje cells counts in the cerebella of four autistic subjects: initial findings of the UCLA-NSCA autopsy research report. Am J Psychiatry 1986;143:862-6.
4. Bauman ML. Microscopic neuroanatomic abnormalities in autism. Pediatrics 1991;(Suppl. 87):791-6.
5. Kemper TL, Bauman ML. The contribution of neuropathology studies to the understanding of autism. Neurol Clin 1993;11: 175-87.
6. Kemper TL, Bauman ML. Neuropathology of infantile autism. J Neuropathol Exper Neurol 1998;57:645-52.
7. Bailey A, Luthert P, Bolton P, Le Couteur A, Rutter M, Harding B. Autism and megalencephaly. Lancet 1993;341:1225-6.
8. Bauman MI, Kemper TL. Neuroanatomic observations of the brain in autism: a review and future directions. Int J Neurosci 2005;23:183-7.
9. Filipek PA, Richelme C, Kennedy DN, Rademacher J, Pitcher DA, Zidel SY, et al. Morphometric analysis of the brain in developmental language disorders and autism. Ann Neurol 1992; 32:475.
10. Piven J, Arndtet S, Bailey J, Havercamp S, Andreasen NC, Palmer P. An MRI study of brain size in autism. Am J Psychiatry 1995; 152:1145-9.

11. Piven J, Arndt S, Bailey J, Arndt S, Bailey J, Andreasen N. Regional brain enlargement in autism: a magnetic resonance imaging study. J Am Acad Child Adolesc Psychiatry 1996;35:530-6.
12. Lainhart JE, Piven J, Wzorek M, Landa R, Santagelo SL, Cook H, et al. Macrocephaly in children and adults with autism. J Am Acad Child Adolesc Psychiatry 1997;36:282-90.
13. Bailey A, Luthert P, Bolton P, Le Couteur A, Rutter M, Harding B. Autism and megalencephaly. Lancet 1993;341:1225-6.
14. Rumsey JM, Duara R, Grady C, Rapoport JL, Margolin RA, Rapoport SI, et al. Brain metabolism in autism. Resting cerebral glucose utilization rates as measured with positron emission tomography. Arch Gen Psychiatry 1985;42:448-55.
15. Horwitz B, Rumsey JM, Grady CL, Rapoport SI. The cerebral metabolic landscape in autism. Intercorrelations of regional glucose utilization. Arch Neurol 1988;45:749-55.
16. Heath RG, Harper JW. Ascending projections of the cerebellar fastigial nucleus to the hippocampus, amygdala and other temporal lobe sites; evoked potential, and histological studies in monkeys and cats. Exp Neurol 1974;45:268-87.
17. Leinar HC, Leiner AL, Dows RS. Cerebrocerebelar learning loops in apes and human. Ital J Neurol Sci 1987;8:425-36.
18. Peterson SF, Fox PT, Posner MI, Mintum MA, Raichle ME. Positron emission tomographic studies in processing of single words. J Cog Neurosci 1989;1:153-70.
19. Akshoomoff NA, Courchesne EA. A new role for the cerebellum in cognitive operations. Behav Neurosci 1992;106:731-8.
20. Schmahmann JD. An emerging concept. The cerebellar contribution to higher function. Arch Neurol 1991;48:1178-87.
21. Bauman ML, Kemper TL. Neurobiology of autism. Baltimore: Johns Hopkins University Press, 1994.
22. Courchesne E, Yeung-Courchesne R, Press GA, Hesselink JR, Jeringan TL. Hypoplasia of cerebellar vermal lobules VI and VII in autism. N Engl J Med 1988;318:1349-54.
23. Hashimoto T, Tayama M, Murakawa K, Yoshimoto T, Miyazaki M, Harada M, et al. Development of the brain system and cerebellum in autistic patient. J Autism Develop Disord 1995;25: 1-18.
24. Piven J, Saliba K, Bailey J, Arndt S. An MRI study of autism the cerebellum revisited. Neurology 1997;49:546-51.
25. Piven J, Arndt S, Bailey J, Andreasen N. Regional brain enlargement in autism: a magnetic resonance imaging study. J Am Acad Child Adolesc Psychiatry 1996;35:530-6.
26. Garber HJ, Ritvo ER. Magnetic resonance imaging of the posterior fossa in autistic adults. Am J Psychiatry 1992;149:245-7.
27. Holttum JR, Minshew NJ, Sanders RS, Phillips NE. Magnetic resonance imaging of the posterior fossa in autism. Biol Psychiatry 1992;32:1091-101.
28. Schafter BG, Thompson JN, Bodensateiner JB. Hipoplasia of the cerebral vermix in neurogenetic syndromes. Ann Neurol 1996; 38:382-5.
29. Ciesielski KT, Knight JE. Cerebellar abnormality in autism: a non-specific effect of early brain damage? Acta Neurobiol Exp (Warsz) 1994;54:151-4.
30. Courchesne E, Sayito O, Townsend JP, Yeung-Courchesne R, Press GA, Lincon AJ. Cerebellar hypoplasia and hyperplasia in infantile autism. Lancet 1994;343:63-4.
31. Hauser SL, De Long GR, Rosman NP. Pneumographic findings in the infantile autism syndrome: a correlation with temporal lobe disease. Brain 1975;98:667-88.
32. Bauman ML, Kemper TL. Neuroanatomical observations of the brain in autism. En: Bauman ML, Kemper TL, editores. Neurobiology of autism. Baltimore: the Johns Hopkins University Press, 1994; p. 119-45.
33. Rapin I, Katzman R. Neurobiology of autism. Ann Neurol 1998;43:7-14.
34. Bachevalier J. Medial temporal lobe structures and autism: a review of clinical and experimental findings. Neuropsychologia 1994;32:627-48.
35. Piven J, Bailey J, Ranson BJ, Arndt S. No difference in hippocampus volume detected on magnetic resonance imaging in autistic individuals. J Autism Develop Disord 1998;28:105-10.
36. Ryu YH, Lee JD, Yoon PH, Kim DI, Lee HB, Shin YJ. Perfusion impairments in infantile autism on technetium-99m ethyl cysteinate dimmer brain single-photon emission tomography: comparison with findings on magnetic resonance imaging. Eur J Nucl Med 1999;26:253-9.
37. Haznedar MM, Buchsbaum MS, Metzger M, Solimando A, Spiegel-cohen J, Hollander E. Anterior cingulate gyrus volume and glucose metabolism in autistic disorder. Am J Psychiatry 1997; 154:1047-50.
38. Rumsey JM, Duara R, Grady C, Rapoport JIL, Margolin RA, Rapoport SI, et al. Brain metabolism in autism. Resting cerebral glucose utilization rates as measured with positron emission tomography. Arch Gen Psychiatry 1985;42:448-55.
39. Gillberg IC, Bjure J, Uvebrant P, Vestergren E, Gillberg C. SPECT (single photon emission computed tomography) in 31 children and adolescent with autism and autism like conditions. Europ Child Adolesc Psychiatry 1993;2:50-9.
40. George MS, Costa DC, Ocurris K, Ring HA, Ell PJ. Cerebral blood flow abnormalities in adults with infantile autism. J Nerv and Mental Dis 1992;180:413-7.
41. Haznedar MM, Buchsbaum MS, Wei TC, Hof PR, Cartwright C, Bienstock CA, et al. Limbic circuitry in patients with autism spectrum disorders studied with positron emission tomography and magnetic resonance imaging. Am J Psychiatry 2000;157: 1994-2001.
42. Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. J Child Psychol Psychiatry 1996;37: 51-87.
43. Ozonoff S, Strayer DI, McMahon WM, Filloux F. Executive function abilities in autism and Tourette syndrome: an information processing approach. J Child Psychol Psychiatry 1994;35:1015-32.
44. Damasio AR, Mauer RG, Damasio AR. Computerised tomographic scan findings in patients with autistic behaviour. Arch Neurol 1980;37:504-10.
45. Damasio AR, Mauer RG. A neurological model for childhood autism. Arch Neurol 1978;35:777-86.
46. Zilbovicius M, Garreau B, Samson Y. Delayed maturation of the frontal cortex in childhood autism. Am J Psychiatry 1995;152: 248-52.
47. Baron-Cohen S, Ring H, Moriarty J, Schmitz B, Costa D, Ell P. Recognition of mental state terms: clinical findings in children with autism and a functional neuroimaging study of normal adults. Br J Psychiatry 1994;165:640-9.

48. Happe f, Ehlers S, Fletcher P, Frith U, Johansson M, Gillberg C, et al. Theory of mind in the brain. Evidence from a PET scan study of Asperger syndrome. Neuroreport 1996;8:197-201.
49. Ozonoff S, Cook I, Coon H, Joseph RM, Klin A, McMahon WM, et al. Perfomance on Cambridge Neuropsychological Test Automated Battery subtest sensitive to frontal lobe function in people with autistic disorder: evidence from the Collaborative Programs of Excellence in Autism network. J Autism Develop Disord 2004;34:139-50.
50. Ohnishi T, Matsuda H, Hashimoto T, Kunihiro T, Nishikawa M, Uema T, et al. Abnormal regional cerebral blood flow in childhood autism. Brain 2000;123:1838-44.
51. Innocenti GM, Manzoni T, Spidalieri G. Patters of the somesthetic messages transferred through the corpus callosum. Exp Brain Res 1974;2919:447-66.
52. Pandya DN, Karol EA, Heilbronn D. The topographical distribution of interhemispheric projections in the corpus callosum of the rhesus monkey. Brain Res 1971;32:31-43.
53. De Lacoste MC, Kirkpatrick JB, Ross ED. Topography of the human corpus callosum. J Neuropathol Exp Neurol 1985;44: 578-91.
54. Manes F, Piven J, Vrancic D, Nanclares V, Plebst C, Starkstein SE. An MRI study of the corpus callosum and cerebellum in mentally retarded autistic individuals. J Neuropsychiatry Clin Neurosci 1999;11:470-4.
55. Egaas B, Courchensne E, Saitoh O. Reduced size of corpus callosum in autism. Arch Neurol 1995;52:794-801.
56. Piven J, Bailey J, Ranson BJ. An MRI study of the corpus callosum in autism. Am J Psychiatry 1997;154:1051-6.
57. Sears LL, Vest C, Mohamed S, Bailey J, Ranson BJ, Piven J. An MRI study of the basal ganglia in autism. Prog Neuropsychopharmacol Biol Psychiatry 1999;23:613-24.
58. Chugani DC, Muzik O, Behen M, Rothermel R, Janisse JJ, Lee J, et al. Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. Ann Neurol 1999;45: 287-9.