Tracing back to the onset of abnormal head circumference growth in Italian children with autism spectrum disorder

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ABSTRACT

This retrospective study aims to describe head circumference (HC) developmental course during the first year of life in 50 Italian children with autism spectrum disorder (ASD) and in a control group of 100 typically developing children (TD). To this end, we use anthropometric measurements (HC, body height, body weight) obtained at birth (T0), 1–2 months (T1), 3–5 months (T2) and 6–12 months (T3) from paediatricians and reported in the infant's 'baby book'. Data indicate that at T2 and T3 HC was significantly greater in ASD group compared to TD, while from T1 weight was significantly smaller in ASD subjects compared to healthy infants. After controlling for weight and height, ASD HC shows an excessive rate of growth from birth. The abnormal HC growth is present in the majority of infants with ASD and could represent a biomarker that together with other clinical signs might promote an early ASD identification.

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1. Introduction

An early autism spectrum disorder (ASD) identification is the prerequisite for a timely intervention that could, in its turn, positively influence long-term outcome (Matson, Wilkins, & González, 2008). To date, the lack of reliable biological markers for identifying ASD has led researchers to concentrate only on behavioral anomalies in order to detect early symptoms of autism (Matson, Rieske, & Tureck, 2011). However, an abnormally large head circumference (HC) represents an intriguing sign in children with ASD, first highlighted by Kanner in his original description of autistic syndrome (Kanner, 1943). Subsequently, several retrospective, prospective and postmortem studies have reported increased incidences of macrocephaly (HC greater than two standard deviations above the mean for a child's age and sex) with different percentages comprised among 14% (Lainhart et al., 1997), 18% (Davidovitch, Patterson, & Gartside, 1996), 24% (Stevenson, Schroer, Skinner, Fender, & Simensen, 1997), and 37–42% (Bailey et al., 1993). Neuroimaging data confirmed the brain enlargement as the most consistent structural magnetic resonance imaging (MRI) finding in ASD toddlers (see for a recent review Chen, Jiao, & Herskovits, 2011). On the basis of the literature, it has thus been suggested that macrocephaly may represent a clinical marker for subtyping individuals with ASD into homogeneous subgroups which can be useful for genetic analyses (Carmichael & McGue, 1995; Losh, Sullivan, Trembath, & Piven, 2008; Maes, Neale, & Eaves, 1997; Silventoinen, Kaprio, Lahelma, & Koskenvuo, 2000).

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More recently, different studies have signalled that macrocephaly, even if common in ASD, is not usually present at birth. For example, two recent retrospective and prospective fetal ultrasound reports of brain size (Hobbs et al., 2007; Whitehouse, Hickey, Stanley, Newnham, & Pennell, 2011) have suggested that HC was not abnormal during fetal development in children subsequently diagnosed with an ASD. Because macrocephaly seemed to develop after birth, regular observations of HC and of its growth rate between seriate measurements during early stages of life, has become the object of many investigations (Elder, Dawson, Toth, Fein, & Munson, 2008; Fukumoto et al., 2008, 2011; Gillberg & de Souza, 2002; Hazlett et al., 2005; Mills et al., 2007; Webb et al., 2007).

Courchesne, Carper, and Akshoomoff (2003) provided, in their pioneeristic work, retrospective information about the course of brain growth during the first year of life. These authors have described the early HC developmental course of 15 preschoolers with ASD compared to 15 healthy infants founding out a smaller HC at birth, followed by an accelerated growth such that by 6–14 months 53% of the sample showed macrocephaly. The finding of the early overgrowth, with a subsequent decline of trajectory has now been replicated by several independent research groups (Dawson et al., 2007; Dementieva et al., 2005; Deutsch & Joseph, 2003; Dissanayake, Bui, Huggins, & Loesch, 2006; Fukumoto et al., 2011; Lainhart et al., 2006). Also recent reports on younger siblings of ASD patients, a population with an higher genetic risk of developing ASD than typical children, have found an association between enlarged HC growth rate and early emerging symptoms (Elder et al., 2008).

Nevertheless, some findings are in contrast with the report of an early increased HC growth in ASD. For example, van Daalen and colleagues (2007) conclude that in ASD there is a dysregulation of growth in general, rather than a dysregulation limited to brain growth; a recent research (Rommelse et al., 2011) describes an accelerated growth of height not only in ASD children, but also in other childhood psychiatric disorders, while an investigation among Israeli ASD children reveals the absence of macrocephaly in this population (Davidovitch, Golan, Vardi, Lev, & Lerman-Sagie, 2011). Moreover, the longitudinal analysis of HC growth in a community-based sample do not indicate the presence of abnormally larger HC in ASD compared with typically developing subjects (TD) (Barnard-Brak, Sulak, & Hatz, 2011). Other studies do not confirm either the finding of abnormally small head size at birth (Dementieva et al., 2005; Gillberg & de Souza, 2002; Lainhart et al., 1997; Mraz, Green, Dumont-Mathieu, Makin, & Fein, 2007; Torrey, Dhavale, Lawlor, & Yolken, 2004) or the positive association of HC overgrowth with measures of autism symptom severity (Dementieva et al., 2005; Torrey et al., 2004). Thus, research seems to indicate that head growth abnormalities are present in only a subpopulation of ASD, both in terms of a larger head circumference and an atypical acceleration of growth. It is possible that for this specific ASD group there is a peculiar growth pattern (Hultman, Sparen, & Cnattingius, 2002): at birth, they appear to have a normal, or even decreased head circumference and only after some months there is an increase in the rate of HC growth (Amaral, Schumann, & Nordahl, 2008; Courchesne et al., 2003; Dementieva et al., 2005; Stevenson et al., 1997). Nevertheless, cautions are warranted: first of all, we do not know yet how many children undergo this abnormal brain growth trajectory, since studies have analyzed differences only in terms of groups; second, prospective data to assess its potential predictive validity are at the initial stage (Elder et al., 2008); third, not always correlation with body length and weight were considered. Finally, there is still no consensus about when HC enlargement is first displayed. Since during the first years of life HC correlates well with brain size (Hazlett et al., 2005), it has been suggested that this phenomenon could reflect an abnormal acceleration of postnatal brain growth processes. If this hypothesis will be confirmed by longitudinal MRI studies examining trajectories of brain development from birth, an accelerated head growth could become an early biological marker for ASD. Currently, the only longitudinal MRI data are related to toddlers from about two years of age (Hazlett et al., 2011; Schumann et al., 2010), but future prospective studies on younger siblings of ASD patients, followed from birth through multiple MRI scans, could shed light on the neuropathological alterations at an earlier stage. In fact, although some authors have argued that an excess of cortical neurons and/or glial cells (Courchesne et al., 2001) and alteration of cell microcolumns (Casanova, Buxhoeveden, Switala, & Roy, 2002) causes early brain overgrowth, the exact pathophysiology of this process remains to be established. Experimental studies have documented that possible consequences of an early overgrowth of the brain could be an alteration of connectivity (Ringo, 1991) resulting in an excess of short-distance cortical connectivity and a reduction of long-distance connectivity (Courchesne et al., 2007). This peculiar brain disconnection is hypothesized to be the neural substrate of ASD core symptoms, as confirmed by some diffusion tensor imaging (DTI) studies on altered structural connectivity in individuals with ASD (e.g. Barnea-Goraly et al., 2004; Lee et al., 2007; Sundaram et al., 2008).

The current paper aims to describe HC developmental course in the first 12 months of life in a relatively large group of Italian children with ASD and to explore possible associations between this developmental process and later clinical characteristics.

2. Methods

2.1. Participants

Fifty preschoolers (40 males and 10 females; mean age: 52 months, SD = 2.1 months) with idiopathic ASD were consecutively recruited between November 2007 and November 2009 among ASD patients referred to the second level Centre for Autism at the Stella Maris Scientific Institute in Pisa. Inclusion criteria were (1) normal term birth (gestational age between 37 and 42 weeks) and (2) paediatric data records reporting head circumference (HC), height (H) and weight (W). In particular, similarly with Courchesne data (Courchesne et al., 2003), we collected anthropometric measurement concerning four age periods: birth (T0); 1–2 months (T1); 3–5 months (T2) and 6–12 months (T3).

All children met criteria for autistic disorder (AD: $n = 20$) or pervasive developmental disorder not otherwise specified (PDDNOS: $n = 30$). ASD diagnosis was made according to the DSM-IV-TR criteria (APA, 2000) by a multidisciplinary team

Table 1
Sample description.

Total sample	ASD (N = 50)	TD (N = 100)
Gender (male/female)	40/10 (ratio 4:1)	80/20 (ratio 4:1)
Age (months)	Mean: 52 (DS: 2.1)	Mean: 52 (DS: 1.7)
Diagnosis	PDDNOS: n = 30 (60%)	
	AD: n = 20 (40%)	
Cognitive functioning	IQ ≥ 70: n = 29 (58%)	
	IQ < 70: n = 21 (42%)	
ASD way of onset	Regressive onset: n = 11 (22%)	
	Early onset: n = 39 (78%)	

ASD, autism spectrum disorder; TD, typically developing children; PDDNOS, pervasive developmental disorder not otherwise specified; AD, autistic disorder.

including a senior child psychiatrist, an experienced clinically trained research child psychologist and a speech-language pathologist during 5–7 days of extensive evaluation, confirmed by the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al., 2002) in 36 of 50 patients and supported by an high Childhood Autism Rating Scale (CARS; Schopler, Reichler, & Renner, 1988) score (≥37, range 37–51) in the remaining 14 subjects. ASD patients performed also the recommended laboratory tests to rule-out medical causes of ASD, including audiometry, thyroid hormone disorders, high-resolution karyotyping, DNA analysis of FRA-X and screening tests for inborn errors of metabolism (plasma and urine aminoacid analysis, urine organic acid measurement, urine mucopolysaccarides quantitation, plasma and urine creatine and guanidinoacetate analysis).

HC, H and W of ASD patients were compared to the same measurements of 100 typically developing (TD) children (mean age: 52 months, SD = 11.7 months). This sample included 80 males and 20 females and was a subset of a healthy paediatric population living in the metropolitan area of Pisa (Tuscany). A non clinical Child Behaviour Checklist 1–5 (CBCL) (Achenbach & Rescorla, 2000) Total score <50 was assumed as an index of typical behavioral development for this healthy group. A description of the samples collected is presented in Table 1.

All the anthropometric measurements (ASD and TD) were obtained by paediatricians during regular well-babies visits. In these schedules of check-ups, the paediatrician checked the general growth development and recorded the infant's height, weight and HC in the infant's 'baby book'. The correspondent percentiles of the measurements were obtained by using the CDC growth charts (NCHS, 2000). The HC (measured in centimeters) was evaluated placing a flexible, non-stretchable measuring device around the largest area of the head (occipital–frontal circumference). At the moment of data collection none of the children had been yet diagnosed with an ASD.

2.2. Instruments

Cognitive development was assessed by the Leiter International Performance Scale-Revised (Leiter-R) (Roid & Miller, 1997) and/or Wechsler Scales (Wechsler, 1973, 1986) according to the patient's age and linguistic level. On the basis of IQ subjects were separated into two groups: IQ < 70 and IQ ≥ 70. Regressive onset of autistic symptoms was evaluated through the Italian version of the Early Development Questionnaire (EDQ) (Ozonoff, Williams, & Landa, 2005).

The research protocol was approved by the Institutional Review Board of the Clinical Research Institute for Child and Adolescent Neurology and Psychiatry.

2.3. Statistical analyses

Statistical analyses were performed using SPSS statistical software version 15 (SPSS Inc., Chicago, III). HC, H and W measures were normalized across sex and age by converting to z scores based on the CDC growth charts (2000). Using the t-test, HC, H and W were compared between ASD subjects and TD individuals at each considered period.

Repeated-measures analyses of variance were carried out to analyze rate growth in HC, H and W between the two groups (ASD and TD).

In ASD subjects, t-test was used to compare HC measurements at four periods: 1 – between males and females; 2 – between AD and PDD-NOS diagnosis; 3 – between IQ levels (IQ < 70 and IQ ≥ 70); 4 – between type of onset (early vs. regressive). Because of the small sample size, repeated-measures analysis of variance was not used to analyze the rate growth of HC between the aforementioned groups (1–2–3–4).

The effect sizes were calculated using the Cohen's d. An absolute value for Cohen's d of 0.50 was considered to have a medium effect and an absolute value for Cohen's d of 0.80 a large effect size (Cohen, 1988).

3. Results

Table 2 shows between-group differences in HC, H and W at four time points.

Table 2
Differences between ASD and TD at each period on HC, weight and height (values are converted to z scores).

	ASD (n = 50)		TD (n = 100)		t-Test	p	Effect size
	Mean	SD	Mean	SD			
HC							
T0	−0.49	0.55	−0.35	0.59	−1.41	0.160	−0.24
T1	−0.31	0.53	−0.28	0.79	−0.16	0.867	−0.04
T2	0.12	0.69	−0.19	0.99	2.04	**0.042***	**0.36**
T3	0.74	0.83	0.37	1.06	2.14	**0.033***	**0.39**
Weight							
T0	−0.48	0.90	−0.34	1.04	−0.82	0.409	−0.14
T1	−0.33	0.86	0.21	0.87	−3.62	<**0.001***	**−0.62**
T2	0.06	0.68	0.39	0.88	−2.35	**0.020***	**−0.42**
T3	0.02	0.76	0.34	1.00	−1.97	**0.050***	**−0.36**
Height							
T0	0.18	0.82	0.29	0.72	−0.83	0.407	−0.14
T1	0.06	0.75	0.05	1.04	0.03	0.970	0.01
T2	0.52	0.84	0.22	1.05	1.77	0.078	0.31
T3	0.58	0.87	0.62	1.36	−0.19	0.843	−0.03

ASD, autism spectrum disorder; TD, typically developing children; HC, head circumference; *$p \leq 0.05$.

3.1. Head circumference

At birth (T0) there was no significant difference in HC size between ASD and TD groups. Specifically, the ASD group was composed of 5/50 children (10%) with microcephaly (HC lower than two standard deviations below the mean for the age and sex); 15/50 children (30%) with HC between 5th and 25th percentile; 30/50 (60%) with HC greater than 25th percentile. TD group was composed of 5/100 children (5%) with microcephaly; 22/100 (22%) children with HC between 5th and 25th percentile; 73/100 (73%) with HC greater than 25th percentile ($\chi^2 = 2.93$, $p = 0.230$).

At 1–2 months (T1) no significant differences in HC size was still present between ASD and TD groups. At 3–5 months (T2) HC was significantly greater in ASD compared to TD (mean value was located at 55th percentile in ASD group, and at 43th percentile in TD group).

At 6–12 months (T3) HC was significantly greater in ASD group compared to healthy infants (mean value was located at 75.8th percentile in ASD group, and at 65.5th percentile in TD group). At T3, macrocephaly (HC > 97th percentile) was present in 9/50 (18%) infants with ASD and in 9/100 (9%) infants with TD. This difference does not reach significance ($\chi^2 = 2.56$, $p = 0.110$).

In ASD group, 10/50 infants (20%) had not increasing developmental course of HC: 7/50 (14%) showed a course similar to TD group, and 3/50 (6%) showed a decreasing course with HC values at T3 lower than at T0.

3.2. Weight and height

There is no significant difference between the height in ASD and TD groups for all four considered periods (Table 2), and no significant differences were found between the two groups ($F = 0.47$, $p = 0.491$) on the rate of height growth.

While the weight was similar at T0, it was significantly smaller in ASD group compared to TD at T1 (36.5th percentile *vs.* 58th), at T2 (52.5th percentile *vs.* 65th) and at T3 (51th percentile *vs.* 63th) (see Table 2). However, no difference was found on the rate of weight growth ($F = 0.20$, $p = 0.655$) between the two groups. Analogous results were obtained when males were separated from females.

3.3. Head circumference growth rate

Repeated measures analysis of variance, controlling for weight and height, shows that over time the rate of HC increases in both groups ($F = 127.42$, $p < 0.001$), but the HC growth was significantly greater in ASD compared to TD group ($F = 11.60$, $p = 0.001$) (Fig. 1). The results for males only reflect the findings for the combined group.

3.4. Relationship between head circumference and ASD characteristics

No significant differences were found in the HC at all time points when comparing the ASD subjects subtyped for gender, diagnosis, IQ level and onset type (see Table 3).

4. Discussion

The purpose of the present study was to supervise the timing of HC development in the first year of life in Italian children with ASD. Our report confirms that the majority of children with ASD display an increased acceleration of HC growth during
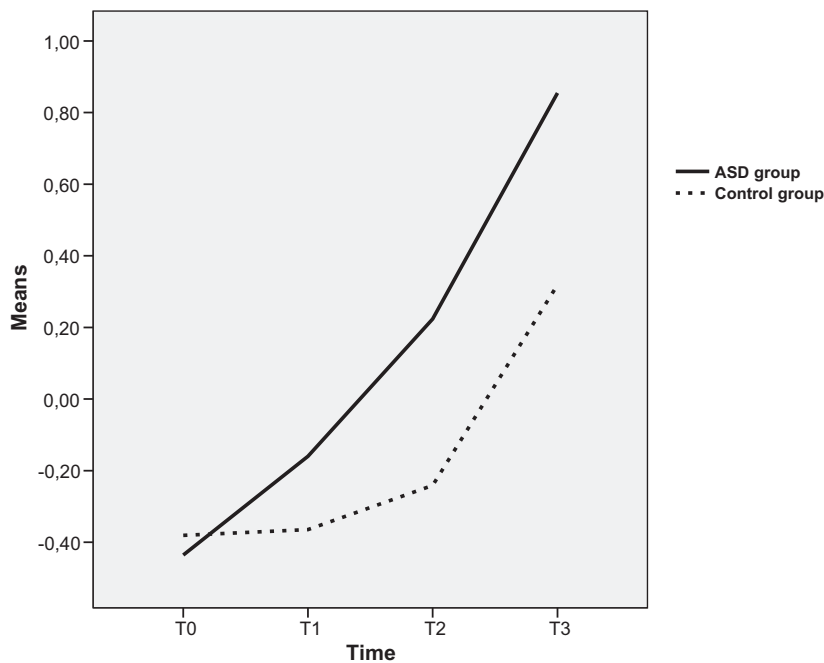
HC: head circumference; ASD: autism spectrum disorder;
TD: typically developing children

Fig. 1. Changes of the *z* score for HC during the first 12 months of life (T0 = birth) in ASD group and TD control group, after controlling for weight and height.

Table 3
ASD group: differences for gender, diagnosis, IQ level and type of onset on HC at four considered periods.

	Subjects (50)	T0 (birth)	T1 (1–2months)	T2 (3–5 months)	T3 (6–12 months)
Gender					
Males	40	-0.53 ± 0.73	-0.22 ± 0.90	0.20 ± 1.09	0.78 ± 1.23
Females	10	-0.19 ± 0.35	-0.005 ± 0.85	0.15 ± 1.01	0.79 ± 0.81
p		0.045	0.491	0.898	0.979
Effect size		-0.59	-0.25	0.05	-0.01
Diagnosis					
AD	20	-0.56 ± 0.68	-0.17 ± 0.86	0.13 ± 1.0	0.50 ± 0.96
PDD-NOS	30	-0.40 ± 0.70	-0.18 ± 0.92	0.24 ± 1.12	0.98 ± 1.25
p		0.435	0.967	0.725	0.156
Effect size		-0.23	0.01	-0.10	-0.43
IQ level					
IQ ≥ 70	29	-0.42 ± 0.64	0.02 ± 0.66	0.18 ± 0.86	0.86 ± 0.96
IQ < 70	21	-0.53 ± 0.76	-0.46 ± 1.08	0.21 ± 1.32	0.68 ± 1.40
p		0.585	0.073	0.930	0.609
Effect size		0.15	0.54	-0.03	0.15
Onset type					
Early	39	-0.40 ± 0.67	0.09 ± 0.91	0.28 ± 1.09	0.95 ± 1.13
Regressive	11	-0.67 ± 0.73	0.49 ± 0.78	-0.12 ± 0.97	0.21 ± 1.08
p		0.267	0.191	0.268	0.062
Effect size		0.38	-0.47	0.39	0.67

ASD, autism spectrum disorder; HC, head circumference; PDDNOS, pervasive developmental disorder not otherwise specified; AD, autistic disorder.

the first 12 months of life. Because some studies have suggested that an increase in the rate of head growth could be the result of an overall increase in body growth of ASD children (Dawson et al., 2007; Fukumoto et al., 2008; van Daalen, Swinkels, Dietz, van Engeland, & Buitelaar, 2007; Torrey et al., 2004), we have controlled HC for weight and height. After this correction, HC begins to grow quickly and excessively from 1–2 months to 3–5 months, reaching the 75.8th percentile at 6–12 months. This result is slightly different compared to first Courchesne study (2003) where the abnormal growth reached the 84th percentile and HC at birth was significantly smaller in ASD group compared to subjects with typical development. In agreement with several other reports (Dementieva et al., 2005; Hultman et al., 2002; Lainhart et al., 1997; Torrey et al., 2004), our ASD newborns show a HC measurement similar to typical control. Second, our findings indicate that the first semester of life represents the period at which the abnormal brain overgrowth has his peak (assuming that HC is a reliable indirect

measure of brain size: Bartholomeusz, Courchesne, & Karns, 2002); during the second semester of life the autistic brain continues to be significantly larger but without any other gain compared to TD. It seems that something causing an abnormal growth occurs during the first semester of life and not during the latter part of the first year as signalled by other authors (Elder et al., 2008). Then, our research proposes that the first semester of life should be considered a specific sensible period for the starting of the disorder: not before the birth when HC is not larger than in TD and not in the slope from 6 to 12 months when the rate of growth is similar to TD. Evidence for the first six months of life as a critical window for autistic onset come also from behavioral findings: retrospective home videotape analysis (Maestro et al., 2001) of infants later diagnosed as having ASD reveals an incipient phase of developmental alteration which displays itself in early differences in social attention. Literature indicates that an early abnormal brain growth process precedes the full expression of the disorder and coincides with the first appearance of subtle behavioral abnormalities (Courchesne, 2004). In fact, prospective studies on children subsequently diagnosed as ASD agree that a clear expression of an altered social behavior is not likely to be found before 12 months of age (Bryson et al., 2007; Landa & Garrett-Mayer, 2006; Zwaigenbaum et al., 2005).

We could suggest that combining measures of HC with behavioral (and/or instrumental) tests for early social and non-social attention might improve our capacity of screening autism at an earlier age. In our study, the HC overgrowth was present in the whole sample except 10 (20%) patients who did not present the growth acceleration regardless the value of HC at birth and regardless the presence of regression. Then, even if an altered HC growth has the potential to be included in a check-list for screen the autism in infancy, we have to take into consideration that this sign is not able to recognize all subjects at risk for autism (Lainhart, 2006). For the ASD subgroup without an early HC acceleration, we should imagine a different pathophysiologic pathway that remains to be elucidated in future studies. According to percentages reported in the recent literature (included between 14% and 34% of cases), we have found macrocephaly (HC > 97th percentile) in 18% of the ASD sample at 6–12 months. This condition is clinically, although no significantly, more present in ASD then in our TD control sample. We could suggest that this is another different group of children with autism characterised by an accelerated growth of HC without reaching the macrocephaly. Thus, three subtypes of children that differ in terms of abnormal HC growth can be individuated in ASD group: (1) abnormal early HC growth with macrocephaly (18% of our patients); (2) abnormal HC growth without final macrocephaly (68% of the sample); (3) absence of abnormal HC growth (14% of children with ASD). Further research is needed to establish whether these different groups could delineate potential ASD phenotypes useful for genetic and neurobiological studies.

We have also examined whether a trajectory of abnormal ASD brain growth is associated with severity of clinical presentation. Previous reports indicate contrasting results: Dementieva et al. (2005) found a correlation between an increased rate of head growth and higher levels of adaptive functioning; on the contrary, in the Courchesne's report (2003), HC at 6–14 months was significantly greater in autistic disorder than in pervasive developmental disorder not otherwise specified and in a multicentric investigation (Lainhart et al., 2006) greater HC was associated with more severe social impairment. In the current study, we have not found any significant difference between these two groups as far as HC at different point is regarded. Furthermore, mean head circumference z scores were not significantly associated with IQ, gender or regressive onset.

Because this is the first paper on Italian children, we can hypothesize that some of the differences between previous studies regarding HC and our results could be related to a different genetic background. First, the weight was significantly smaller in ASD *vs.* TD: in contrast to this finding, several other researchers (Davidovitch et al., 1996; Fukumoto et al., 2008, 2011; Mraz et al., 2007) have reported that body weight, as well as HC, was significantly bigger in ASD babies. On the other hand, underweight represents a frequent feature among older ASD individuals (Al-Farsi et al., 2011; Bölte, Özakara, & Poustka, 2002; Mouridsen, Rich, & Isager, 2002). Second, our study has pooled males and females because no gender difference was found in HC; differently, Fukumoto and co-authors (2008) considered boys and girls as two different groups and pointed out that body weight was significantly increased in Japanese males with autism. Third, unlike other researchers (Dissanayake et al., 2006; Torrey et al., 2004) who reported a general abnormal growth of the body sizes including the stature, in our study mean length z scores did not differ significantly from controls at any age interval. For these different reasons, we propose that in future studies it will be considered appropriately HC together with body measures using similar ethnic group as we did.

There are limitations to this study that merit some discussion. The homogeneity of the sample in terms of provenances (the whole sample – ASD and TD – was composed of Caucasian children of Italian descent) prevents to extend conclusions to the entire population with ASD. Moreover, the incomplete clinical assessment (lack of ADOS in 13 of 50 ASD patients) limits the correlation between cardinal symptoms of ASD and HC measurements. In addition, since ASD sample is composed of children both with and without mental retardation, there are differences between patients and TD controls regarding IQ that could play a role on present findings. Further studies that recruit an additional idiopathic mental retardation sample are therefore warranted in order to claim our data as specific of an ASD and not of a more general developmental delay. Finally, the retrospective nature of the present work has reduced the possibility to collect a broad ASD sample with all anthropometric available data (HC, H and W) for all four periods (T1, T2, T3 and T4).

5. Conclusions

In conclusion, based on the results of this study, an abnormal HC growth rate is documented in the first 12 months of life in children with ASD and tracing back to the onset, the excessive increase in head size emerges around the third months of life. Although ASD and frank macrocephaly co-occur only in a limited number of ASD children, our data corroborate the

importance to measure the HC in children in the first months of life because its abnormal rate of growth, in addition to other behavioral signs, could contribute to the process of early ASD identification.

Conflict of interest statment

Acknowledgements

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