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Setback phenomenon in autism and long-term prognosis

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R. Kobayashi[1], T. Murata[2]

[1]Department of Social Work, Tokai University School of Health Sciences, Kanagawa and [2]Faculty of Education, Kyushu University, Fukuoka, Japan

From among the subjects of a follow-up study on cases of autism conducted by the authors in 1990, 179 cases for which precise records were available on the infancy period were selected for evaluation of the relationship between the occurrence of setback phenomenon in infancy and long-term prognosis. The following results were obtained: (i) a significantly higher rate of epilepsy among the setback group compared to the non-setback group; and (ii) a significantly lower level of language development among the setback group upon entering elementary school compared to the non-setback group, although the difference between the present levels of adaptation of the two groups was not significant. Factors determining the long-term prognosis of the setback group are discussed.

Key words: autism; long-term prognosis; regression; setback phenomenon; speech loss

Ryuji Kobayashi, Department of Social Work, Tokai University School of Health Sciences, Bohseidai, Isehara, Kanagawa, 259–1193 Japan

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Introduction

Among the various types of autism, cases that have undergone normal or close-to-normal development before onset, but afterwards exhibit regressive changes affecting overall development—known as setback-type autism (1, 2)—are believed to constitute approximately one-third of all cases of autism. Regressive changes noted in this type of autism (hereafter referred to as the setback group) include loss of interest in the outside world and accompanying loss of speech in early infancy. Similarities to disintegrative psychosis (ICD-9) (3) have been pointed out, given its characteristic process of development (4). Moreover, in the field of paediatric neurology, although the Landau-Kleffner syndrome in which language regression is exhibited after epileptic seizure is a well-known phenomenon, the relationship between the setback phenomenon and epilepsy/epileptic EEGs has yet to be clarified (5).

Many reports have noted a poor prognosis for the setback group (1, 2, 6–8). On the other hand, although some have reported higher levels of development for late-onset autism, in which autistic symptoms appear later than in early-onset autism (9–11), this is believed to be more a reflection of the mildness of the autistic symptoms, which leads to a delay in detecting the developmental abnormality (12).

Kurita (4) asserts the distinctiveness of the setback group together with disintegrative psychosis from the non-setback group in terms of causative factors from an aetiological standpoint. Analysis of the long-term prognosis provides a vital clue for evaluating whether or not the setback group is an entity which should be regarded as a group of its own within autism, and also for determining the characteristics of the disorder.

However, most studies that have followed up on the process of development have been extended only through puberty or adolescence, at which time the subjects are still undergoing development (11, 13, 14). Studies following the cases through to adulthood, when a relatively stable mental state is reached, are almost non-existent. In view of the fact that puberty and adolescence constitute the period during which such patients, like normal individuals, are most easily disturbed both mentally and physically, it is readily apparent that following the setback group beyond that period is indispensable for better clarification of their prognosis.

For this reason, the author has attempted to re-evaluate the issue of long-term prognosis of the setback group, based upon previously published findings from a follow-up study of 201 cases of autism (15).

Table 1. Life events precipitating setback phenomenon

Life event	*n*	Onset of setback phenomenon (age in months)[a]
Mother's hospitalization	1	24
Mother caring for a sibling during illness	1	18
Mother in part-time work	1	20
Mother's withdrawal	1	12
Birth of siblings	2	35, 40
Participation in a funeral	1	41
Moving house	4	18, 28, 30, 36
Sexual harassment by a boy	1[b]	8
High fever	2	7, 12
Self-poisoning	1	12
Intussusception	1	42
Pseudo-cholera	2	8, 19
Gas poisoning	1	13
Electric shock from electric wire	1	24

[a] Three cases were unspecified.
[b] Female case.

Material and methods

Subjects

For the present study, 179 cases (151 males and 28 females) for whom precise records were available on the infancy period were selected from among the 201 subjects of the above-mentioned follow-up study of children with autism (15).

Clinical evaluation of all subjects was conducted by the two authors (R.K. and/or T.M.) in the clinical setting. Cases of paediatric neurological disease (organic brain disease, progressive neurological disease, etc.) and Rett's syndrome were excluded from the study. One case of hearing loss was noted.

The clinical diagnoses for all subjects satisfied the diagnostic criteria for autistic disorder according to DSM-III-R (16).

The mean age (±SD) at first visit of the 179 cases was 6.1±2.6 years. The range of duration of follow-up (excluding the 3 deceased patients) was 6.5–28.4 years, with a mean duration (±SD) of 15.8±3.9 year. Age at first visit was less than 6 years in over two-thirds (121 of 179) of the cases, and over 90% (162 of 179) of the subjects were under 9 years old.

The mean age (±SD) of subjects at the time of the study was 21.9±3.2 years (minimum 18 years, maximum 33.2 years), excluding 3 patients who had died.

Methods

Interviews for obtaining information on the life histories of the subjects in infancy were conducted by the two diagnosing physicians who also carried out the clinical evaluations. The physicians interviewed the parents (mainly the mothers) of all subjects with regard to the time period when the subjects started to exhibit autistic conditions, and the presence of any life events which might have triggered the onset.

Identification of the setback phenomenon was made by determination of the regressive changes affecting overall development, including loss of uttered words in early infancy accompanied by loss of interest in the outer world, despite having undergone normal or close-to-normal development before onset, and the continuation of this pathological state for longer than a minimum period of 3 months.

Results

Incidence of the setback phenomenon and gender differences

Among the 179 cases, 53 subjects (29.6%) were classified in the setback group, consisting of 42 males (27.8%) and 11 females (39.3%), showing a slightly higher propensity of occurrence among females, although the difference was not statistically significant.

Age of onset of the setback phenomenon

Age of onset of the setback phenomenon among the 53 cases representing the setback group revealed only 3 cases with onset before age 1 year, the highest number—25 cases—with onset between ages 1 and 2 years, 17 cases with onset between 2 and 3 years, and 8 cases with onset after the age of 3 years. There was no significant difference in age of onset between males and females. The 3 cases with onset before age 1 year were all females, and although utterance of words was not determined at the time, they were included in the setback group according to the criteria for identification referred to previously, as they came to exhibit regressive changes affecting overall development and accompanying loss of interest in the outside world triggered by some particular life event.

Life events precipitating the setback phenomenon (Table 1)

The existence of some life event believed to have triggered the setback phenomenon among the 53 setback cases was noted in 20 cases (37.7%). The particular life events and the age (in months) of onset of the setback phenomenon are listed in Table 1. The majority of life events of significance were, specifically, the mother's absence (due to

Table 2. Setback phenomenon and onset of epilepsy

	Onset of epilepsy[a]				
	Yes (n=33)		No (n=135)		
Setback phenomenon	n	%	n	%	Total (n=168)
Setback type	15	31.3	33	68.7	48
Non-setback type	18	15.0	102	85.0	120

[a] 11 cases were unknown: $\chi^2=5.74$, df=1, $P<0.01$.

hospitalization, looking after sick members of the family, work commitments, etc.), the mother's withdrawal due to poor mental health, the birth of siblings, and changes in the environment, e.g. as a result of moving to a different part of the country. Other causes included serious physical illness of the child (e.g. pseudo-cholera, intussusception, auto-intoxication), and unique episodes such as electrical shock caused by biting through an electric flex.

The setback phenomenon and perinatal complications

With regard to perinatal complications, the incidence of abnormality in the gestational (38 of 172 subjects; 22.1%) or neonatal period (31 of 170 subjects; 18.2%) was around 20% for both groups, showing no statistically significant difference. However, the incidence of natal complications (53 of 171 subjects; 31.0%) was significantly higher among the non-setback group (43 of 118 subjects; 36.4%) than in the setback group (10 of 53 subjects; 18.9%). Complications during the pregnancy period included surgery, premature amniorrhexis, severe hyperemesis, threatened abortion, and severe amenia. Complications noted during parturition included premature delivery, overdue delivery, labour induction, vacuum extraction, forceps delivery, and enwrapped umbilical cord. Problems in the neonatal period included severe jaundice, neonatal asphyxia, and weakness in suckling, among others.

The setback phenomenon and level of intelligence at 6 years

Intelligence levels on reaching school age (6 years) were evaluated primarily by the Binet or Wechsler intelligence tests, although in some cases they were determined through overall clinical evaluation. Comparison of intelligence levels between the setback and non-setback groups in terms of IQ above (33 of 56 subjects) or below 50 (20 of 69 subjects) yielded significantly lower results for the setback group ($\chi^2=4.54$, df=1, $P<0.05$).

The setback phenomenon and onset of epilepsy

Onset of epilepsy (see Table 2) was noted in 33 of the total of 168 cases (excluding 11 unknown cases), which corresponds to an incidence rate of 19.6%. In terms of the setback phenomenon, epilepsy was seen in 31.3% (15 of 48 subjects) of the setback group, and in 15.0% (18 of 120 subjects) of the non-setback group, showing a significantly higher incidence among patients in the setback group ($\chi^2=5.74$, df=1, $P<0.01$).

The setback phenomenon and level of language development at 6 years

The results are shown in Table 3. Seven of 53 cases (13.2%) in the setback group exhibited more than

Table 3. Setback phenomenon, language development level at age 6 years, present language developmental level (PLDL) and present adaptive level (PAL)

	Language development level at age 6 years[a]			PLDL[b]			PAL[c]		
	Good	Fair	Poor	Good	Fair	Poor	Good	Fair	Poor
Setback phenomenon	(n=33)	(n=55)	(n=90)	(n=83)	(n=56)	(n=37)	(n=45)	(n=50)	(n=81)
Setback type	7	11	35	16	24	11	10	16	25
Non-setback type	26	44	55	67	32	26	35	34	56

[a] One case was unknown: $\chi^2=7.25$, df=2, $P<0.05$. Levels of speech development at 6 years were defined as good (can speak naturally with a rich vocabulary or can speak, although unnaturally and sometimes inappropriately), fair (can speak, although with echolalia) or poor (vocalizes only with echolalic speech or does not vocalize any meaningful words).

[b] Three patients who died were excluded: $\chi^2=9.05$, df=2, $P<0.05$. Present language development level (PLDL) was defined as good (can communicate freely with a rich vocabulary or can communicate, although unnaturally and sometimes inappropriately), fair (can understand others in daily life, but cannot communicate verbally) or poor (vocalizes with echolalic speech mostly in single words, or vocalizes 'words' with no meaning, or does not talk).

[c] Three patients who died were exluded: $\chi^2=1.36$, df=2, non-significant. Present adaptive level (PAL) was identified as good (employed (or goes to school) and adapts satisfactorily, his or her ability to work is highly estimated, or employed (or goes to school), lives a normal life almost independently), fair (behaves a little inappropriately, but is capable of leading a normal daily life at home, or not employed but capable of living normal daily life with a little assistance), or poor (behaves very oddly, cannot adapt socially, and requires some assistance, or has poor social skills, cannot adapt socially, always in need of much assistance).

Table 4. Onset of setback phenomenon, present language development level (PLDL) and present adaptive level (PAL)

	PLDL[a]			PAL[b]			
Onset of setback phenomenon	Good ($n=16$)	Fair ($n=24$)	Poor ($n=11$)	Good ($n=10$)	Fair ($n=16$)	Poor ($n=25$)	Total ($n=51$)
Before age 2 years	10	12	6	6	9	13	28
After age 2 years	6	12	5	4	7	12	23

[a] $\chi^2=0.61$, df=2, non-significant.
[b] $\chi^2=0.20$, df=2, non-significant.

fair (i.e. very good or good) levels of language development, compared to 26 of 125 cases (20.8%) in the non-setback group, which was a significantly lower result ($\chi^2=7.25$, df=2, $P<0.05$).

The setback phenomenon and present language development level (PLDL)

The results are shown in Table 3. More than fair development (very good or good) was seen in 31.4% (16 of 51 cases) of the setback group, and in 53.6% (67 of 125 cases) of the non-setback group, showing a significantly lower level of development for the setback group ($\chi^2=9.05$, df=2, $P<0.05$).

The setback phenomenon and present adaptive level (PAL)

The results are shown in Table 3. More than fair levels of adaptation (very good or good) were seen in 19.6% (10 of 51 cases) of the setback group, and in 28.0% (35 of 125 cases) of the non-setback group, showing no significant difference between the two groups ($\chi^2=1.36$, df=2, non-significant).

Period of onset of the setback phenomenon and present level of development

The results are shown in Table 4. The authors have taken particular note of the fact that the difference in the period of onset of the setback phenomenon appeared to have a strong influence on the subsequent process of development (7, 17). Differences between onset before and after 2 years of age merit particular attention. In that context, the setback group was evaluated by dividing the group into those subjects with onset before and after the age of 2 years, in order to determine the relationship between period of onset and present level of development. However, the results revealed no significant difference in either PLDL ($\chi^2=0.61$, df=2, non-significant) or PAL ($\chi^2=0.20$, df=2, non-significant) between the two groups. Analysis according to age group using cut-off points other than the age of 2 years also gave similar results.

Discussion

Aetiological classification of the setback group within autism

Today, the international diagnosis of autism is based upon systems of classification such as the DSM-III-R (16) or ICD-10 (18), but the diagnostic classification for autism has undergone extensive change with each revision of these systems. Of particular importance among such changes is the question of age of onset. The ICD-9 (3)and DSM-III (19) had established the age of onset as occurring before 30 months, but this was revised to before 36 months in ICD-10, while the age of onset was itself removed from among the essential stipulations of the diagnostic criteria in DSM-III-R, relegating the issue to the status of one of the specified items. Because onset of behaviour characteristics peculiar to autism is seen not only in infancy but also thereafter in more than a few cases (9, 20), age of onset is no longer deemed to be a point of great significance as a diagnostic criterion in autism.

On the other hand, problems pertaining to the subclassification of autism have attracted much attention in recent years. The existence of a setback group has been a focus of attention in our country from early on (1, 2), and has been a topic of detailed study to date, but this idea is also gaining increasing recognition in Europe and the USA. The momentum of the debate as to what, if any, differences exist between the group of cases with autism undergoing normal or close-to-normal development for some time after birth, but thereafter exhibiting regression in terms of development (i.e. the cases referred to as disintegrative psychosis (ICD-9) or disintegrative disorder (ICD-10)), and those cases of autism with onset shortly after birth, is gradually increasing (4, 11, 21, 22).

Kurita (22) regards the setback group as being closely related to disintegrative psychosis, while asserting the need for reassessment of aetiological concepts, given the existence of a transitional form leading on to childhood schizophrenia. In addition, in analysing the differences between the setback

group and disintegrative psychosis, Kurita et al. (14) have focused on the difference in developmental level between the onset of the setback phenomenon and the mode of reaction to psychosocial stress, and they have surmised that the higher sensitivity of cases of disintegrative psychosis to stress may be due to their higher level of development before onset.

From studies on the setback phenomenon in two pairs of siblings exhibiting congruous autistic disorders, Kobayashi & Fujiyama (17) have placed great emphasis on the level of developmental pathology of internal object relationships, focusing on the great disparity in the developmental process and clinical picture depending on the period of onset.

Both researchers highlight the difference in age of onset as one of the primary factors determining the subsequent pathological picture. However, further investigation of the relationship between the setback group and disintegrative psychosis at this point requires identification of the disorder at as early a stage as possible, and more detailed analyses predicated on the clinical picture and long-term course (4).

Findings from the present analysis

The subjects of the present study were those for whom sufficient data was available on the infancy period from among 201 cases who had been observed through long-term follow-up by the authors. As reported elsewhere (15), these subjects do not deviate greatly in terms of distribution of intelligence level from that of previously published reports (23). Among this group, the proportion of the setback group was 29.6%, a result which is also quite similar to the findings of previous reports (2, 5, 6, 8, 24, 25). The number of subjects, amounting to 53 cases in the setback group, is among the largest reported in previous studies. For these reasons, it is believed that the reliability of the present survey on evaluation of the long-term prognosis for these subjects can be regarded as being quite high, even though it is largely dependent on retrospective data.

Period of onset and life events precipitating the setback phenomenon. Burd et al. (21, 26) have proposed subclassification of pervasive disintegrative disorder (designated as such by Burd et al.) (21) exhibiting regression from some point in development into the Rett and Heller types, pointing out the earlier age of onset in females than in males.

The results of the present study indicate no statistically significant difference in age of onset between the sexes, although all cases with onset of setback phenomenon before the age of 1 year were female, and a greater number of cases with onset after the age of 3 years were male. It is of interest that Burd et al. (26) have focused their attention on the fact that regression appears to occur at an earlier stage in females than in males. However, in view of the results of the present study, this aspect appears to merit further analysis.

The involvement of psychosocial factors in the onset of the setback phenomenon has been pointed out from the start (2). Our study also revealed the involvement not only of environmental factors (such as being subjected to separation from the mother or to changes in living environment), but also of individual factors (such as the patient's own physical disorders or physical stress). The present study also indicated the involvement of psychosocial factors at a frequency comparable to that cited in other reports (6, 8, 25). However, as the life events considered in our study were retrospective data in addition to that being obtained from the parents, determination of the role that these factors may have played in triggering the setback phenomenon was difficult.

Relationship between the setback phenomenon and epilepsy. The present study was conducted by child psychiatrists, with the primary characteristic being length of the observation period. Although neurological specialists were not specifically involved in evaluating the EEG findings, cases of acquired epileptic aphasia (Landau-Kleffner syndrome) and paediatric epileptic syndrome, which fall within the category of childhood neurological disorders, were not included among the subjects of this study.

As yet there is no consensus regarding the incidence of EEG abnormalities in comparing the setback group or disintegrative psychosis with the non-setback group, with some authors claiming a higher incidence (4), while others have reported a lower incidence (27). There are also discrepancies regarding previous history of epileptic disorder, for which a higher incidence is reported by some researchers (6), while others have reported no difference (5, 11).

The results of the present study indicate a significantly higher rate of 31.3% for epilepsy among the setback group, which is more than a twofold higher rate of incidence compared to the non-setback group. Bearing in mind the fact that most epilepsy has an onset in puberty or adolescence, with a higher risk of onset until adulthood (15), it can be stated that evaluation of epilepsy requires a considerable length of follow-up. The fact that Tuchman & Rapin (5) reported no difference in

the rate of epilepsy between the two groups could very well arise from the difference in the duration of follow-up. From that point, too, our results appear to be indicative of the extent of involvement of organic factors in the setback group.

Perinatal complications were also considered in this study, although no noteworthy difference was observed for the setback group. On the contrary, the results revealed a higher incidence of natal problems for the non-setback group. Perinatal complications are not indicative of brain damage *per se*, but further studies are required to allow interpretation of these results.

As demonstrated by the present findings, because psychosocial factors such as life events appear to be intricately intertwined with biological factors in the setback phenomenon, perhaps it can be concluded that its onset may also be triggered by the complex interaction not only of the biological factors but also of the psychosocial factors as well.

Onset of the setback phenomenon and course of previous development. As cited in previous reports to date (1, 4, 6, 25), our study also revealed significantly lower levels of language development at age of entry into elementary school and at present in the setback group. However, there was no particularly significant lowering of levels with regard to present level of adaptation.

It is true that many cases of setback phenomenon or disintegrative psychosis display difficulty in recovery, but this does not mean that such cases continue to regress pathologically indefinitely, and it has been pointed out that some of the cases display a good recovery after a short period of regression (2).

Kobayashi (7) has deduced from analysis of the relationship between differences in the period of onset and the subsequent process of development that, in onset after the age of 2 years, subjects are more prone to unstable and easily disturbed object relationships, which are in turn more likely to be reflected in the developmental process later on. This was regarded as arising from instability in object constancy at that stage in ego development due to difficulty in cognition of total representation, even though the subjects are capable of recognizing partial representation. Subsequently, Kobayashi & Fujiyama (17) evaluated differences in the period of onset of the setback phenomenon and clinical picture in four cases of siblings with congruous autistic disorders all exhibiting the setback phenomenon. In that study, they observed that differences in the clinical picture of provocative behaviour could be a reflection of differences in the levels of development of object relationships. Through these studies, Kobayashi & Fujiyama (17) have asserted the possibility that pathology of internal object relationships of the autistic child may be largely disparate depending upon the level of development acquired before the onset of the setback phenomenon.

Kurita et al. (14) have pointed out that, in cases of disintegrative psychosis, the patients are probably in a state of readiness to respond sensitively to psychosocial stress because their level of development before the onset of disintegrative psychosis is relatively higher, suggesting the likelihood that the timing of onset of pathological regression is reflected in the state of subsequent disease.

These findings, taken together with the fact that the degree of autism has been considered to be milder in Heller syndrome than in autism (28, 29), appear to be important indications for explaining the diversity in the developmental process after onset in relation to the level of development before onset.

However, the results of the present evaluation of the long-term prognosis indicate that, although a difference in the timing of onset of the setback phenomenon did, to a certain extent, determine intellectual level in the long term, it was not a determinant of overall prognosis, including the aspect of adaptation. How may this discrepancy be interpreted?

First, we must consider the methodological limitations of research in which chronological age is taken as the only index for capturing period of the onset in the setback phenomenon, mental disorders in infancy, or developmental disorders. In other words, this discrepancy may be an indicator of the problems and limitations inherent in employing chronological age as the reference standard in attempting to capture stages of development from the viewpoint of systematic development.

Secondly, the process of development of setback-type autism undergoes a major period of transition in puberty and adolescence. Needless to say, this is not peculiar to setback-type autism. However, given that the developmental process in setback-type autism is particularly prone to turbulent fluctuation (7, 17), it is not unlikely that measures taken in response to such subjects in puberty and adolescence may determine their subsequent course of development. Because the course of development of autistic children can not only take a turn for the worse, but may equally well show marked improvement in puberty and adolescence (15), it can probably be said that the results of the present study also point, albeit indirectly, to the crucial importance of the way in which such subjects are dealt with in those periods.

Classification of the setback phenomenon and issues for future study

A general review of the studies of the setback phenomenon or disintegrative psychosis to date appears to indicate that this group of disorders, taken together, does not point to simple further pathological progression of some cerebral biological factor.

The onset of the setback phenomenon is a problem of critical significance, not only in terms of the period of infancy, but also in terms of the onset of psychosis *per se*. Kurita (22) has made a vital remark pointing to the need for re-evaluation of schizophrenia and pervasive developmental disorder as being disparate disorders, given that there is a transitional type to both, in which a disintegrative psychosis-like state is exhibited.

Today, autism and psychosis are generally accepted as disparate developmental disorders. However, the group of developmental disorders that exhibit the setback phenomenon is in itself a problem lending support to the need for a complete reassessment of the relationship between autism and psychosis. Kobayashi (30, 31) has propounded the perception metamorphosis phenomenon as one of the key concepts in pursuing the relationship between autism and schizophrenia, but clarification of the relationship between such phenomena and the setback phenomenon is another aspect that warrants further study.

At this point, caution is required when discussing whether a phenomenon such as perception metamorphosis is an entity which denotes the setback phenomenon, but in view of the fact that a good recovery is seen in more than a few cases of setback-type autism, it is believed that early and specific therapeutic intervention in infants who display the setback phenomenon may very well determine the outcome for these patients.

Hitherto, therapeutic relationships with setback group cases have mostly been initiated after the passage of considerable time from the appearance of the setback phenomenon. It may be concluded that, at this point, there is a pressing need for clinical practice focusing on how we are to detect the emergence of setback phenomenon and provide crisis intervention at as early a stage as possible, in order to clarify the mechanism of onset and to establish therapeutic methodology specific to the disorder.

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