PAPER

Neurological abnormalities in young adults born preterm

M Allin, M Rooney, T Griffiths, M Cuddy, J Wyatt, L Rifkin, R Murray

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See end of article for authors' affiliations

Correspondence to: Dr Matthew Allin, Section of General Psychiatry, Division of Psychological Medicine, Box 063, Institute of Psychiatry, De Crespigny Park, London, SE5 8AF, UK; matthew.allin@iop.kcl.ac.uk

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Objective: Individuals born before 33 weeks' gestation (very preterm, VPT) have an increased likelihood of neurological abnormality, impaired cognitive function, and reduced academic performance in childhood. It is currently not known whether neurological signs detected in VPT children persist into adulthood or become attenuated by maturation of the CNS.

Method: We assessed 153 VPT individuals and 71 term-born controls at 17–18 years old, using a comprehensive neurological examination. This examination divides neurological signs into primary and integrative domains, the former representing the localising signs of classical neurology, and the latter representing signs requiring integration between different neural networks or systems. Integrative signs are sub-divided into three groups: sensory integration, motor confusion, and sequencing. The VPT individuals have been followed up since birth, and neonatal information is available on them, along with the results of neurological assessment at 4 and 8 years of age and neuropsychological assessment at 18 years of age.

Results: The total neurology score and primary and integrative scores were significantly increased in VPT young adults compared to term-born controls. Within the integrative domain, sensory integration and motor confusion scores were significantly increased in the VPT group, but sequencing was not significantly different between the VPT and term groups. Integrative neurological abnormalities at 18 were strongly associated with reduced IQ but primary abnormalities were not.

Conclusions: Neurological signs are increased in VPT adults compared to term-born controls, and are strongly associated with reduced neuropsychological function.

Individuals born before 33 gestational weeks (very preterm, VPT) are more likely than their term-born peers to exhibit neurological and neuropsychological impairments and to do less well at school. This is likely related to the increased risk of brain injury in VPT individuals.[1–5] Neurological impairments have been found to be more common in preterm and low birth weight children[6–10] and range in severity from impairments with disability (such as sensorineural hearing loss, amblyopia, and spastic tetraplegia, hemiplegia, or paraplegia) to lesser impairments not associated with disability.[7] These lesser impairments have been reported to include agnosias, apraxias, tone or reflex asymmetry, poor coordination of fine movements,[6] dystonia, dysdiadochokinesis, and mirror movements.[11] In a recent follow-up study, Foulder-Hughes and Cooke[12] assessed 280 VPT children and found that rates of neurological abnormality varied from 24 to 42% depending on the test used, suggesting that the neurological abnormalities found in VPT children are heterogeneous and may be fully elucidated only by a comprehensive neurological examination. Few studies have followed up VPT individuals into adulthood, and it is therefore not clear whether neurological abnormalities persist into adult life or are attenuated by ongoing maturation of the CNS. It is also not clear whether neurological abnormalities in adulthood are associated with impairments in other domains, such as cognitive functioning.

This study aimed to follow up a cohort of VPT 18 year olds and compare them to full-term born control 18 year olds with a detailed and comprehensive clinical neurological examination. The primary prediction was that VPT 18 year olds would show more neurological abnormalities than the term-born control group. We further predicted that neurological abnormalities would be associated with reduced neuropsychological performance in adulthood.

METHODS

Study groups

VPT group

The potential study group consisted of 318 individuals born before 33 weeks' gestation and admitted between 1979 and 1983 to University College Hospital London (UCLH) Neonatal Unit within 5 days of birth. They were enrolled into a prospective study of outcomes of preterm birth. Assessments of neurological and cognitive development were performed at 1 and 4 years of corrected age (that is, the age the child would have been if the pregnancy had actually gone to term) and at 8 and 14 years of age. At 17–18 years of age, 154 individuals (48%) from this cohort were assessed. Those who were assessed at 18 years of age did not differ significantly from those who were not assessed in paternal social class ($\chi^2 = 2.56$; df = 5; $p = 0.768$), birth weight ($t = -0.781$; df = 316; $p = 0.436$), gestational age ($t = 0.202$; df = 316; $p = 0.840$), or gender ($\chi^2 = 0.374$; $p = 0.541$).

Term-born comparison group

Fifty three infants who were delivered at term (38–42 weeks) at University College Hospital from 1979 to 1980 had been enrolled as age matched controls for assessments made on the VPT cohort at 4 years of age. These individuals were contacted at the same time as the VPT group and 18 agreed to take part in the study. A further 55 term-born, normal birthweight individuals were recruited from advertisements in the local and national press. The control group thus consisted of 73 individuals.

Abbreviations: UCLH, University College Hospital London; VLBW, very low birth weight; VPT, very preterm

Neurological instrument

VPT and term-born individuals were assessed blind to status by one of two investigators (MA or MR). The neurological assessment procedure followed that of Griffiths *et al*[13] and is a modified version of the Neurological Evaluation Scale of Buchanan and Heinrichs.[14] A scoring instrument was used to rate a structured clinical neurological examination (table 1). The examination proceeded in a stereotyped order. Each item was given a rating of 0, 1, or 2 (0 = no abnormality, 1 = mild abnormality, 2 = definite abnormality). The instrument is divided into primary and integrative signs. Primary signs are those that may be elicited by a traditional neurological examination. They include cranial nerve abnormalities, asymmetry of limb reflexes, and eye movement abnormalities. Integrative signs are those that are likely to require integration within the motor system, or between the motor and sensory systems. They are likely to depend on distributed processing involving more than one neural network and are not localising in the same way as the primary signs. They have often been referred to as soft neurological signs. The integrative signs are further divided into sensory integration, motor confusion, and sequencing domains (table 1).

Inter-rater reliability

Ratings were performed by MA and MR, who completed inter-rater reliability testing by independently rating video assessments made by a third investigator (TG). Inter-rater reliability between MA and MR was: total neurology, $\alpha = 0.97$; primary signs, $\alpha = 0.99$; integrative signs, $\alpha = 0.96$.

Neuropsychological assessment

Neuropsychological testing was performed at 18 years of age, using a short (five subtest) form of the Wechsler Adult Intelligence Scale–Revised (WAIS-R).[15 16]

Statistical analysis

The neurological instrument produced a score which did not follow a normal distribution in either the VPT or term groups, with clustering of values around zero. Transformations of the data did not yield a normal distribution. The Mann-Whitney U test was used to compare the two groups. χ^2 or Fisher's exact test was used for comparison of categorical data between groups. Associations between neurological outcome and other data were explored using Kendall partial correlation analyses controlling for social class and age at assessment.

Table 1 Individual neurological signs in the primary and integrative domains of the neurological assessment instrument

Primary measures	Integrative measures
Cranial nerve palsy R	Sensory integration
Cranial nerve palsy L	Stereognosis R
Smooth pursuit	Stereognosis L
Saccade to target	Graphaesthesia R
Saccade to command	Graphaesthesia L
Synkinesis	Extinction
Gaze impersistence R	R-L confusion
Gaze impersistence L	Motor confusion
Convergence R	Tandem walk
Convergence L	Rapid alternating movements R
Tone increase R	Rapid alternating movements L
Tone increase L	Finger-thumb opposition R
Hypereflexia R	Finger-thumb opposition L
Hypereflexia L	Finger-nose R
Plantar R	Finger-nose L
Plantar L	Motor sequencing
Romberg's sign	Fist-ring R
Chorea R	Fist-ring L
Chorea L	Fist-edge-palm R
Tremor R	Fist-edge-palm L
Tremor L	Oszeretski
Mirror movements R	
Mirror movements L	
Glabellar tap	
Suck	
Grasp	
Snout	

L, left; R, right.

RESULTS

Study subjects

One VPT case was excluded as he had had an episode of meningitis 4 years previously which had been associated with a period of coma. Two control subjects were excluded as one had suffered a significant head injury as a child and the other had a history of birth complications on more detailed assessment.

Therefore 153 VPT cases and 71 controls were included in the analysis. The VPT group was slightly, but significantly, younger when assessed, and had lower IQ. The VPT group had increased rates of left and mixed handedness, although this difference did not reach statistical significance. The groups did not differ significantly in gender distribution, but there was a significant difference in social class distribution (table 2). Since socioeconomic disadvantage is known to adversely affect developmental outcome in preterm and low birth weight children,[17] social class and age at assessment were used as covariates in the subsequent analyses.

Neurological examination

The total neurological examination score was significantly raised in the VPT group compared to the term group ($U = 3914$; $p = 0.001$) (table 3).

Both primary ($U = 3972$; $p = 0.001$) and integrative ($U = 4250$; $p = 0.008$) subtotals were significantly increased in VPT individuals. Sensory integration ($U = 4321$; $p = 0.005$) and motor confusion ($U = 4248$; $p = 0.003$) subtotals were also significantly higher in the VPT group, but the sequencing subtotal was not significantly different between the two groups.

Distribution of individual neurological signs

For all variables, more VPT individuals were rated deviant than term controls (table 4). The difference was statistically significant for the following measures: left-sided cranial nerve palsy ($\chi^2 = 8.54$; $p = 0.014$), gaze impersistence ($\chi^2 = 5.89$; $p = 0.053$), Romberg's sign (Fisher's exact test = 3.88; $p = 0.044$), left-sided mirror movements ($\chi^2 = 5.81$; $p = 0.055$), right-left confusion ($\chi^2 = 6.24$; $p = 0.044$), and left ($\chi^2 = 7.44$; $p = 0.024$) and right ($\chi^2 = 8.17$; $p = 0.017$) finger-nose co-ordination.

Table 2 Comparison of demographic details of the VPT and term groups

	VPT cases	Term controls
Parental social class		
I	20	23
II	43	20
III	50	21
IV	21	6
V	7	1
Unclassified	8	0*
Males/females	78/75	41/30†
Handedness, % right/left/mixed	83.6/15.0./1.4	92.8/4.3/2.9‡
Age at assessment in years, mean (SD)	17.9 (0.67)	18.5 (1.28)¶
Full scale IQ, mean (SD)	107.0 (15.3)	116.4 (17.8)§

*For statistical comparison, social class was collapsed into two groups, higher (I and II) and lower (III–V and unclassified). χ^2 (1,1) = 5.74; p = 0.017; †χ^2 (1,1) = 0.892; p = 0.389; ‡χ^2 (1,2) = 5.54; p = 0.063; ¶F = 16.17; df = 1,203; p<0.001; §F = 15.24; df = 1,204; p<0.001.

Table 3 Comparison of summed scores on the neurological instrument between cases and controls

	Cases, mean (range)	Controls, mean (range)	U	p
Total neurology	9.7 (0–40)	6.4 (0–40)	3914	0.001
Primary subtotal	5.3 (0–25)	3.4 (0–22)	3972	0.001
Integrative subtotal	4.5 (0–21)	3.1 (0–20)	4250	0.008
Sensory integration	0.8 (0–5)	0.5 (0–4)	4321	0.005
Motor confusion	1.6 (0–10)	0.9 (0–9)	4248	0.003
Sequencing	2.1 (0–10)	1.7 (0–10)	4951	0.249

Gender differences

In the VPT group, there were no significant differences between males and females in neurological examination scores in any of the summed categories. However, in term-born controls, there was a disparity between males and females, such that males had significantly higher total neurological ($U = 435$; $p = 0.035$) and primary signs ($U = 371$; $p = 0.004$) scores than females (table 5).

Associations between neurological abnormalities and perinatal variables

There was no relationship between the total neurology score and either birth weight or gestational age. There was a weak correlation between the motor confusion score and birth weight, and significant negative associations between gestational age and integrative signs, particularly motor confusion (table 6). There were no significant associations between neurology scores at 18 years of age and other perinatal variables, including Apgar scores, time to spontaneous respiration, and indices of acidosis (pH, base excess).

Associations between neurological abnormalities at 18 years of age and IQ scores

Higher total and integrative scores were significantly associated with lower full-scale, verbal, and performance IQ. There were no significant relationships between IQ measures and primary neurological abnormalities (table 7).

DISCUSSION

In this group of VPT young adults, we have demonstrated an increase in neurological abnormalities compared to a term-born control group. Total, primary, and integrative abnormalities were all increased relative to the term group. The VPT group also had increased rates of left or mixed handedness. These results confirm that neurological signs associated with VPT birth persist into adulthood.

The pattern of individual neurological signs may suggest links to underlying pathologies. For example, eye movement abnormalities have been reported in association with periventricular leukomalacia and damage to the optic radiation.[18] Mirror movements were more common in the VPT group, and are an indication of abnormalities of sensorimotor and interhemispheric interaction. They are a normal finding in young children and disappear with maturation, as well as being associated with genetic conditions (Klippel-Feil syndrome, X-linked Kallman syndrome) or occurring as an isolated finding. Mirror movements are also seen after brain damage in early life[19] and occur more frequently in left handers.[20] The anatomical basis for bilateral motor encoding is still debated and may depend on the aetiology of the mirror movements. Maegaki *et al*[21] studied two individuals with congenital mirror movements and concluded that there is bilateral activation of sensorimotor cortex. Others have proposed the existence of extra ipsilateral corticospinal pathways.[22] Still others have proposed that both mechanisms may be acting in the same individuals.[19] The corpus callosum has also been implicated,[20] the theory being that maturational myelination of the corpus callosum allows transcallosal inhibition of the ipsilateral pathways.

The increase in mirror movements in VPT individuals shown here may thus reflect a delay in neurological maturation. The normal mirror movements of childhood would be expected to disappear by 10 years of age,[23] so this would imply a significant motor delay in our VPT 18–19 year olds. If the disappearance of normal mirror movements depends on corpus callosum myelination, it may be that VPT individuals are experiencing a delay in this process. There is considerable evidence that perinatal white matter lesions, in particular periventricular leucomalacia, result in delayed myelination.[24 25] Additionally, the corpus callosum has been shown to be both structurally[26] and functionally[27] abnormal in VPT individuals.

Gaze impersistence, also increased in this VPT group, is another sign that is associated with callosal pathology.

Table 4 Group scores for individual measures

	VPT cases score		Term controls score			
	1	2	1	2	χ^2	p
Primary measures						
Cranial nerve palsy R	6	7	1	0	4.49	0.106
Cranial nerve palsy L	11	6	0	0	8.54	0.014
Smooth pursuit	16	10	6	2	1.64	0.441
Saccade to target	9	1	0	0	4.89	0.087
Saccade to command	6	2	2	0	1.14	0.566
Synkinesis	22	4	9	2	0.12	0.941
Gaze impersistence R	15	3	2	0	4.94	0.085
Gaze impersistence L	17	3	2	0	5.89	0.053
Convergence R	5	1	1	0	1.12	0.571
Convergence L	2	7	0	1	2.39	0.302
Tone increase R	17	7	4	1	3.33	0.189
Tone increase L	19	9	6	1	3.27	0.195
Hypereflexia R	41	11	14	6	1.92	0.383
Hypereflexia L	39	15	13	9	1.59	0.452
Plantar R	9	10	3	1	3.09	0.213
Plantar L	12	12	6	4	0.37	0.832
Romberg's sign	8	0	0	0	3.88	0.044*
Chorea R	20	5	9	1	0.66	0.719
Chorea L	17	8	8	2	0.70	0.706
Tremor R	8	2	1	1	1.84	0.399
Tremor L	8	2	2	1	0.66	0.718
Mirror movements R	35	30	19	5	5.81	0.055
Mirror movements L	45	30	24	7	3.36	0.187
Glabellar tap	31	12	7	5	3.94	0.139
Suck	1	0	0	0	0.47	0.683*
Grasp	1	0	0	0	0.49	0.673*
Snout	0	0	0	0		
Integrative measures						
Sensory integration						
Stereognosis R	2	0	0	0	0.943	0.464*
Stereognosis L	1	0	0	0	0.47	0.683*
Graphaesthesia R	6	0	2	1	2.32	0.313
Graphaesthesia L	10	2	3	0	1.44	0.486
Extinction	3	2	1	0	1.03	0.598
R-L confusion	21	38	9	8	6.24	0.044
Motor confusion						
Tandem walk	5	3	2	1	0.13	0.939
Rapid alternating R	15	9	8	2	1.04	0.593
Rapid alternating L	21	15	9	3	2.19	0.335
Finger-thumb R	14	12	3	4	2.17	0.338
Finger-thumb L	17	18	5	4	3.30	0.192
Finger-nose R	14	4	0	1	7.44	0.024
Finger-nose L	28	5	3	3	8.17	0.017
Motor sequencing						
Fist-ring R	21	14	8	6	0.32	0.854
Fist-ring L	21	22	9	7	1.01	0.604
Fist-edge-palm R	21	15	12	6	0.45	0.799
Fist-edge-palm L	31	20	15	7	0.47	0.790
Oszeretski	26	29	10	9	1.99	0.369

Figures represent the number of individuals in a group scoring 1 or 2 for each measure. Finger-thumb, finger-thumb opposition; L, left; R, right; Rapid alternating, rapid alternating movement.
*p value by Fisher's exact test.

Table 5 Comparison of summed scores on the neurological instrument between male and female term-born controls

	Male, mean (range)	Female, mean (range)	U	p
Total neurology	8.0 (0–40)	4.3 (0–24)	435	0.035
Primary subtotal	4.3 (0–22)	2.1 (0–9)	371	0.004
Integrative subtotal	3.8 (0–20)	2.2 (0–16)	511	0.204
Sensory integration	0.5 (0–4)	0.4 (0–3)	611	0.951
Motor confusion	1.2 (0–9)	0.5 (0–7)	543	0.252
Sequencing	2.0 (0–10)	1.4 (0–10)	526	0.251

Heilman and Adams[28] reported the onset of gaze impersistence after callosal transection (for treatment of epileptic seizures) in a patient with a pre-existing right hemisphere lesion. Bae and Pincus[29] found that periventricular white matter damage (in term-born adults) was associated with abnormalities of visual tracking and with three-step motor sequencing. Gaze impersistence has also been attributed to disordered CNS maturation and occurs with increased frequency among patients with early onset schizophrenia.[30]

The VPT group also had increased rates of right-left (R-L) confusion, which classically occurs in Gerstmann's syndrome (along with finger agnosia, agraphia, and acalculia) in association with lesions of the dominant angular gyrus.[31] R-L confusion is also, of course, an everyday phenomenon recognised by many people who do not have a neurological condition and is reported to be more common in men and in left handers.[32] It is possible that this sign also represents a deficit of interhemispheric information transfer.

We also found an increased rate of neurological signs in the term males compared to term females. This may reflect a general increased susceptibility to neurodevelopmental insult in boys, or that girls are more developmentally robust. There is evidence for a male disadvantage, for example, perinatal mortality for very low birth weight (VLBW) boys is significantly greater than for girls, and surviving boys have a higher risk of adverse outcomes.[33 34] Our results did not show a clear difference in neurological outcome between male and female VPT 18 year olds; in fact, both groups were equally impaired. We therefore cannot rule out the possibility that the difference between male and female controls reflects a bias in our term comparison group. Such a bias would be likely to have reduced the chance of finding differences between the two groups. It should also be pointed out that the term-born comparison group was made up of individuals from two sources: a birth cohort from UCLH and individuals recruited at age 18 from press advertisements.

Table 6 Associations between neurological outcomes at 18 years of age and birth weight and gestational age

	Birth weight	Gestational age
Total neurology	−0.130	−0.130
	p=0.136	p=0.137
Primary subtotal	−0.033	0.009
	p=0.706	p=0.915
Integrative subtotal	−0.156	−0.212
	p=0.073	p=0.014
Sensory integration	−0.018	−0.048
	p=0.838	p=0.586
Motor confusion	−0.177	−0.247
	p=0.042	p=0.004
Sequencing	−0.126	−0.157
	p=0.148	p=0.072

Results of partial correlation analyses (Kendall partial rank correlations) in VPT cases, controlling for age at assessment and social class, showing associations between neurological outcomes at 18 years of age and birth weight and gestational age (df=128).

Table 7 Associations between neurological outcomes and neuropsychological testing at 18 years of age

	Full scale IQ	Verbal IQ	Performance IQ
Total neurology	−0.340	−0.307	−0.250
	p<0.001	p=0.001	p=0.005
Primary subtotal	−0.132	0.078	−0.127
	p=0.148	p=0.392	p=0.165
Integrative subtotal	−0.466	−0.446	−0.328
	p<0.001	p<0.001	p<0.001
Sensory integration	−0.254	−0.265	−0.187
	p=0.005	p=0.003	p=0.039
Motor confusion	−0.422	−0.392	−0.302
	p<0.001	p<0.001	p=0.001
Sequencing	−0.380	−0.364	−0.260
	p<0.001	p<0.001	p=0.004

Partial correlation analyses (Kendall partial rank correlations) in very preterm cases, controlling for age at assessment and social class, showing associations between neurological outcomes at 18 years of age and neuropsychological testing at 18 years of age.

In this group of VPT young adults, we found associations between neurological dysfunction and gestational age, and a weak association with birth weight. This is consistent with Foulder-Hughes and Cooke[12] who reported weak correlations between childhood neurological abnormality and birth weight and gestational age. Perinatal indicators of hypoxia and acidosis showed no significant associations with neurological abnormalities in any domain. This is surprising, in that hypoxia/ischaemia is often assumed to be the cause of many of the brain lesions associated with preterm birth. It may be that the lesions which cause neurological compromise are those that affect white matter (such as periventricular leukomalacia) and are not adequately described by perinatal Apgar scores or blood pH.

There were strong associations between integrative neurological abnormalities and full scale, verbal, and performance IQ at 18 years of age in the VPT group. This is in agreement with the large body of literature that suggests that neurological dysfunction, even if mild, is associated with reduced academic performance. It suggests that neurological signs, possibly of relatively trivial importance in themselves, are potentially markers of a real cognitive disability. Olsen *et al*[35] found that "minor neurodevelopmental dysfunction" in preterm children was associated with reduced neuropsychological performance. Sullivan and McGrath[36] suggested that early motor delay contributes to later cognitive disability and refer to this as "hidden morbidity". Several studies have found that neurological signs in LBW children are associated with reduced IQ and specific learning disabilities.[37 38]

Limitations

We found a relatively high rate of neurological deviance in the term control group. However, estimates of rates of neurological signs in the normal adult population vary widely from 26%[30] to 90%[39] and rates of neurological abnormalities increase with age. In young people there is generally a higher rate of neurological signs, for example Kennard[40] reported neurological signs in 60% of a group of 72 normal children. Buchanan and Heinrichs,[14] using a very similar rating scale to that used here, found rates of abnormalities very similar to those in our study in a control group of 50 healthy adults.

In comparing the frequencies of individual neurological signs between the groups (table 4), we have not made a statistical adjustment to compensate for multiple comparisons. It thus remains possible that some of these findings are due to chance, so caution should be used in their interpretation. For example, the difference between left and right sides

for signs such as cranial nerve palsy and mirror movements may be indicative of chance effects. However, most individual signs are found to be more frequent in the VPT group, regardless of the level of statistical significance.

Another potential weakness of this study is the reliability of assessments of neurological signs.[41] Inter-rater reliability has been shown to be poor for rare signs, for example those occurring in less than 10% of subjects.[13 14] Reliability has been shown in various studies to be lowest for sensory signs,[42] eye movements,[13] and primitive reflexes (grasp, suck, snout).[30] Summing the individual scores, as we have done here, improves their reliability.[42]

A further limitation of this study is the relatively low follow-up rate of the VPT group (48%). This drop out rate is a problem common to many long term follow-up studies[12] and may limit the generalisability of our findings. Additionally, the VPT group was 7 months younger than the term group, and it is not clear how much this might have contributed to group differences. It is certainly known that structural brain changes continue into young adulthood and beyond, including progressive changes in relative amounts and distribution of grey and white matter[43] and in the size of the corpus callosum.[44] However, little is known about changes in neurological signs over this time.

CONCLUSIONS

In summary, we find increased neurological signs in young adults born very preterm. The pattern of signs suggests a deficit of sensorimotor and interhemispheric integration. Neurological dysfunction may be in itself mild, but it is strongly associated with reduced neuropsychological performance and may therefore represent a hidden morbidity in individuals born very preterm.

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Authors' affiliations

M Allin, M Cuddy, L Rifkin, R Murray, Institute of Psychiatry, King's College, London, UK
M Rooney, St Michael's Unit, Mercy University Hospital, Grenville Place, Cork, Ireland
T Griffiths, Regional Neurosciences Centre, Newcastle General Hospital, Westgate Rd, Newcastle upon Tyne, UK
J Wyatt, Perinatal Brain Research Group, Department of Paediatrics, University College London Medical School, London, UK

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